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*Gray, A. L.: Southern Med. J., 43:320, April, 1950.

California MEDICINE

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Antabus and the Metabolism of Alcohol

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SUMMARY

Antabus does not alter the rate of alcohol metabolism in dogs. It interferes with the metabolism of acetaldehyde, so that the ordinarily prompt removal of this substance from the tissues as it is produced in the metabolism of alcohol does not take place.

It seems reasonable to assume that it is this accumulation of acetaldehyde in the tissues in abnormally high concentrations that is responsible for the unpleasant symptoms following the taking of alcohol by a patient receiving antabus.

IT is natural that any agent showing promise in therapy of alcoholism should be enthusiastically acclaimed by both the medical profession and the public at large, and such acclaim has fallen to the new drug, tetraethylthiuram disulfide. Fittingly called antabus, this drug was first employed by a group of Danish investigators, and has had considerably popularity in Scandinavia. During the past two years it has been subjected to clinical trial in this country, much of the work being encouraged by the Council on Pharmacy and Chemistry of the American Medical Association, in an effort to ascertain whether or not it should be released for general use. Since such release has not as yet been forthcoming, it is probable that not all the information so far gathered is favorable.

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Chairman's Address: Presented before the Section on Psychiatry and Neurology at the 79th Annual Meeting of the California Medical Association, April 30-May 3, 1950, San Diego.

The purpose of this presentation is to report the results of an investigation of the effect of the drug on the metabolism of alcohol rather than its clinical effect on alcoholism.

Antabus by itself does not produce any symptoms in the dosages employed but results in very unpleasant symptoms when alcohol is taken as well, and this of course is the basis of the treatment, which consists of maintaining the patient on the dose of antabus adequate to make any alcoholic indulgence too costly in discomfort.

It was noted by the Danish investigators that the symptoms shown by a patient who took alcohol after having been maintained on adequate dosage of antabus resembled closely those reported as resulting from administration of acetaldehyde. It has long been accepted that acetaldehyde is probably an intermediary product in the metabolism of alcohol in the animal body. Small amounts of acetaldehyde are to be found in the blood of normal animals, so it is not a substance foreign to the bodily economy. Supniewski[10] as early as 1927 showed that in the blood of the rabbit there was 0.54 mg. of acetaldehyde per 100 cc., while in normal dogs the content was 0.08 mg. per 100 cc. Handovsky and Heymans[6] found acetaldehyde in normal blood and urine. Furthermore, ingestion of alcohol has been found to increase the acetaldehyde content in the blood significantly. Supniewski[10] gave alcohol in a dose of 2.5 gm. per kg. of body weight to dogs and found acetaldehyde content of 0.75 mg. per 100 cc. of blood, while in rabbits given the same dose the blood content of the drug was 1.5 mg. per 100 cc. Simultaneous administration of insulin about doubled the height of rise of the blood acetaldehyde, and it is known that insulin increases the rate of metabolism of alcohol. Hald and Jacobsen[3] found

that in man ingestion of 40 cc. of alcohol produced a blood acetaldehyde of 0.105 mg. per 100 cc. Thus it would appear that acetaldehyde is formed in the metabolism of alcohol in the body, and that the rate of formation must be sufficiently rapid for some of the substance to accumulate in the tissues and appear in the blood stream. This level is not sufficiently high to produce symptoms, certainly not of the type reported after antabus and alcohol. However, the Danish investigators found that if they administered acetaldehyde intravenously to human subjects they were able, by controlling the rate of injection, to produce symptoms reported by them to be exactly similar to those observed after antabus and alcohol. An infusion rate of 80 mg. per minute, or 4.8 gm. per hour, produced a blood acetaldehyde of 0.7 mg. per 100 cc., while half this amount gave 0.3 mg. per 100 cc. A dose of alcohol adequate to raise the blood alcohol concentration to 50 mg. per 100 cc. produced a blood acetaldehyde of 0.1 mg. per 100 cc. in a normal patient, while Hald and Jacobsen[3] reported that when alcohol was given to a subject who was taking antabus the blood acetaldehyde rose to about 0.5 mg. per 100 cc. Since this is well above the concentration found to produce symptoms, they felt that the evidence was clear that the symptoms produced when alcohol is taken by a patient on antabus are due to an increased level of acetaldehyde in the blood and tissues.

The problem remains as to how the antabus operates to produce this increase in blood acetaldehyde. The two most likely possibilities are an increased production of acetaldehyde and a decrease in the rate of its destruction. As to the first, accepting the theory that all alcohol in its metabolism passes through an initial dehydrogenation to acetaldehyde, the only way for more acetaldehyde to be formed is for more alcohol to be burned. As the rate at which alcohol disappears from the blood stream has been extensively studied and is pretty well understood,[2] any significant change should be easy to determine.

Hald, Jacobsen and Larsen[4] have reported that the rate of alcohol metabolism is unchanged by previous administration of antabus. However, Larsen[7] found that when alcohol was slowly infused into animals premedicated with antabus, the amount of acetaldehyde formed was greater with more rapid rates of infusion. He could not reconcile this finding with the generally held belief that the rate of alcohol metabolism is independent of its concentration in the tissues. The more recent concept that alcohol metabolism is indeed, to some extent at least, influenced by concentration[2] may make this finding more plausible.

There remains the possibility that acetaldehyde, rather than being formed more profusely, is itself metabolized less rapidly in the animal receiving antabus. This should be readily capable of proof, but no well-documented evidence on the point has appeared to date. Hald and Jacobsen[3] referred to some work done by colleagues, but then unpublished, to the effect that acetaldehyde is eliminated in animals on antabus at the same rate as in normal animals. If this finding were accepted, it would make the whole matter of the effect of antabus inexplicable. That was the reason for the investigation here reported.

It has been established[9] that although a single 100 mg. dose of acetaldehyde readily kills a 200 gm. rat by respiratory depression, such an animal may receive doses of 20 mg. at 15-minute intervals until 250 mg. has been given without any symptoms being apparent. It has also been demonstrated[11] that the lethal dose by subcutaneous injection is four times as great as by intravenous injection. All this implies that acetaldehyde is quite toxic, but that destruction of the drug in the body proceeds quite rapidly.

EXPERIMENTAL WORK

Since the metabolism of alcohol in dogs is very similar to the process in man, dogs were chosen as the experimental animal. As protracted intravenous injections were to be done, it was considered expedient to anesthetize the animals with pentobarbital sodium by the intraperitoneal route. This had the disadvantage, however, of obscuring any minor signs of acetaldehyde toxicity, so that the investigation developed no adequate observations on the clinical manifestations of the effect of acetaldehyde in the dogs.

Alcohol in a solution of 10 per cent by volume was infused by gravity into a vein in the leg. Infusion of the dose of 1.0 gm. per kg. of body weight took about 10 minutes. Acetaldehyde was also given intravenously by gravity, a 2 per cent solution being made up by the addition of freshly distilled acetaldehyde to normal saline. Care was taken to keep the container of acetaldehyde cooled by surrounding it with a jacket of ice to minimize loss of this very volatile substance by evaporation during the prolonged injection. This was continued over a period of six hours. On one occasion the rate of injection was 185 mg. per kg. per hour, which represents the maximum reported rate of alcohol metabolism in the dog, while on another it was 100 mg. per kg. per hour, the approximate rate of alcohol metabolism in the dogs involved.

At appropriate intervals blood samples were taken from another vein than that used for the infusion, with heparin as the anticoagulant. All apparatus was previously cooled to avoid loss of acetaldehyde, the sample was immediately refrigerated, and the analysis for acetaldehyde was made within a few hours at most, using the method of Burbridge, Hine and Schick.[1] This method entails delivery of the blood sample into the outer chamber of a Conway microdiffusion unit, the center chamber of which contains a known amount of semicarbazide reagent. Diffusion is allowed to take place for 90 minutes at 28° C., the contents of the central chamber is washed into a test tube graduated at 10 cc., and brought to volume with distilled water, and the optical density at wave length 224 millimicrons determined in the

Beckman spectrophotometer. A calibration curve having been previously prepared by using the same procedure with known concentrations of acetaldehyde, the value of the specimen can be read directly from the curve.

In those experiments in which alcohol was administered, alcohol determinations were done on the same samples, using the method described by Newman[8] with the modification that iodometric titration against standard thiosulfate solution was substituted for the colorimetric procedure as a matter of convenience.

RESULTS

Two mongrel dogs, designated A and C, weighing 10 kg. and 8 kg., were used for all the experiments. A dose of alcohol of 1.0 gm. per kg. was administered intravenously, and samples of blood were taken 30 minutes, one, two, three, four, five, and six hours after the start of the infusion, which required ten minutes.

The rate of decline of blood alcohol concentration, using the period from one to six hours, was 12.2 mg. per 100 cc. per hour for dog A, and 14.4 mg. per 100 cc. per hour for dog C—values in line with previous experience in this laboratory and elsewhere. The blood acetaldehyde concentrations rose slowly during this period, at the end of which the blood alcohol concentration had still not fallen to the base line, being in the vicinity of 50 mg. per 100 cc. The final acetaldehyde concentration was 0.2 mg. per 100 cc. in dog A and 0.36 mg. per 100 cc. in dog C. Thus the findings of previous investigators that administration of alcohol raises the blood acetaldehyde concentration were confirmed, although the results were rather lower than the 0.75 mg. per 100 cc. found by Supniewski[10] in the dog after twice as large a dose of alcohol, and rather higher than the 0.1 mg. per 100 cc. found by Hald and Larsen[5] with a smaller dose.

Next, a slow intravenous infusion of acetaldehyde was given, a rate of 185 mg. per kg. of body weight per hour being chosen because this is the maximum rate at which this species has been shown to metabolize alcohol, and thus would be the maximum rate at which such metabolism might be expected to produce acetaldehyde in the body. There was an initial rapid rise in the content of acetaldehyde in the blood to around 1.5 mg. per 100 cc. with subsequent fall to values comparable to those after infusion of alcohol. It is difficult to account for this initial rapid rise and subsequent decline, which seems to indicate that it takes the body some time to attain full efficiency in acetaldehyde metabolism. When a slower infusion rate of 100 mg. per kg. of body weight per hour was used, equal to the rate of alcohol metabolism in these dogs, there was still an initial rise and later decline, but not to the degree that was observed with the faster rate. It can be said with some assurance that the rate of acetaldehyde metabolism is greater than the rates of infusion used in these experiments, and thus the rate at which acetaldehyde could be formed from alcohol metabolism.

The dogs were then given antabus in dosage rather greater than that recommended for man on a weight basis. They received, by mouth, 0.5 gm. the first day, 0.25 gm. the second, and 0.125 gm. daily thereafter. About a week elapsed after the initial dose before the first experiment with alcohol after antabus was done. This consisted of a repetition of the injection of alcohol in the amount of 1.0 gm. per kg. of body weight. On this occasion the rate of fall of blood alcohol concentration was 14.0 mg. per 100 cc. per hour for dog A and 10.8 mg. per 100 cc. per hour for dog C—well within the range of day-to-day variation in rate of alcohol metabolism. This confirmed the finding that the presence of antabus does not have any significant effect on the rate at which alcohol is metabolized. The blood acetaldehyde values showed a prompt rise to the vicinity of 0.6 mg. per 100 cc., fluctuated considerably, and by the end of six hours, while there was still a considerable concentration of alcohol in the blood, dropped to about 0.05 mg. per 100 cc. of blood, or to a level lower than when the same dose of alcohol was given without antabus. This experiment confirmed the rise in blood acetaldehyde after antabus and alcohol. It indicated further that the level maintained is quite inconstant, and may fall to a low level before all the alcohol disappears. The explanation of this is obscure.

Next, the slow infusion of acetaldehyde at the lower rate, 100 mg. per kg. of body weight per hour, was repeated while the animals were on antabus. There resulted a rise in blood acetaldehyde quite comparable to that seen in the previous experiment with alcohol, indicating that there is no essential difference whether the acetaldehyde is formed by the metabolism of alcohol in the body or is injected into the blood stream. On another occasion a more rapid infusion of acetaldehyde at 185 mg. per kg. of body weight was carried out, and on this occasion there was a progressive rise in blood acetaldehyde to the high figures of 2.0 mg. per 100 cc. of blood in dog A and 4.0 mg. per 100 cc. in dog C. This interference with the metabolism of acetaldehyde by antabus, although striking, is really not very great, since if no acetaldehyde metabolism took place at all, a blood acetaldehyde level of 111.0 mg. per 100 cc. would be expected at the end of the six-hour infusion, whereas the actual average concentration reached was barely 3 per cent of that level. Moreover, the blood acetaldehyde values dropped precipitately in the hour after the infusion ceased, indicating rapid metabolism of acetaldehyde even in the presence of antabus. That this interference, after administration of alcohol in the range reported by the Danish investigators, is sufficient to produce acetaldehyde concentrations great enought to cause symptoms identical with those of acetaldehyde administration has been conclusively demonstrated by the present work. It has also been shown that the effect of antabus is not an acceleration of acetalde-

hyde production, but rather a slowing of the metabolism of acetaldehyde, allowing it to accumulate in the tissues in higher than normal concentrations.

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Antabus in the Treatment of Alcoholism in a Private General Hospital

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SUMMARY

In 35 consecutive cases in which patients were admitted to a private hospital for alcoholism, antabus was contraindicated for eight patients and administered to 27. Sixteen patients, followed three to nine months, cooperated fully with treatment and did not return to use of alcohol. In four cases there was at least one episode of drinking, but the patients continued to cooperate with treatment and attained partial success. In seven cases, including three in which antabus was stopped because of organic disease, treatment was unsuccessful. Insufficient insight and lack of family cooperation accounted for four failures.

The presence of cardiovascular or hepatic diseases contraindicates antabus. As the test of reaction to alcohol after antabus has been given is hazardous, continuous supervision by nurse and physician throughout the test reaction is mandatory.

Sustained results depend upon psychotherapy, family cooperation, careful follow-up, and control of side-reactions to the drug.

Antabus as an antagonist to alcohol is not safe enough to permit general use of the drug.

PREVIOUS extensive experience with the conditioned reflex treatment, prolonged hospitalization with psychotherapy, and the utilization of Alcoholics Anonymous in the management of chronic alcoholism were disappointing from the standpoint of sustained results. This led the authors to investigate Antabuse.® The purpose of this presentation is to report initial clinical experience with antabus in the treatment of alcoholism in a psychiatric department of a general hospital.

As early as 1914 Koelsch[10] discovered that cyanamide produced sensitivity to ingested ethyl alcohol. The fungus *coprinus atramentarius* produces a similar effect.[6]

In 1948 Hald, Jacobsen, and Larsen[7] published preliminary reports in English on the sensitizing effect of tetraethylthiuramdisulfide (antabus) and its use in the treatment of alcoholism. They showed that patients taking appropriate doses of antabus invariably experience extreme physical discomfort following the ingestion of small amounts of ethyl alcohol. As a result of animal and clinical investigation, they attributed this reaction to increased production of acetaldehyde.[6]

After clinical application by these Danish investigators, Jacobsen and Martensen-Larsen[8] reported a high percentage of socially recovered patients, noting that "all persons with alcoholism who have consulted us were treated with antabus and no absolute contraindications have been seen thus far." However, deaths have been reported,[4, 9] with this treatment; and other investigators[1, 5] have listed a number of contraindications and precautions in selection of patients. An editorial[2] in the *Journal of the American Medical Association* summarized recent opinion: "It is apparent that treatment of alcoholism with antabus is far from being free from danger. It should be carried out only in the hospital with small doses of both the drug and alcohol and with all the facilities at hand for emergency resuscitation. The patient should be carefully observed for a number of hours after the acute reaction."

The treatment program used by the authors follows, in general, the recommendations of Glud.[5] As early as possible after the patient is hospitalized the responsible relative is interviewed in order to evaluate the probable extent of family cooperation and obtain a medical and psychiatric history. At this time the relative is informed as to the general nature of the treatment and the necessity of long-term cooperation.

During the first two days in the hospital the patient has complete physical and neurologic examinations along with interviews to establish his psychiatric status and to inform him of the principles of treatment. Intensive psychotherapy is continued throughout hospitalization. Complete blood cell count, serology, and urinalysis are routine. Electrocardiograms are taken if history or physical findings suggest cardiac difficulties. A high protein, high carbohydrate, low fat diet is supplemented by vitamin B complex. After at least two days, glucose tolerance and sulfobromophthalein tests are done. If no more than 15 per cent of the sulfobromophthalein is retained at 30 minutes and if other findings are within normal limits, and the patient's cooperation is assured, antabus is given according to the usual dosage of 2 gm. the first day, 1.5 gm. the second,

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1 gm. the third, and 0.75 gm. on the fourth day. On the fourth day of antabus administration, the patient's reaction to alcohol is tested, under constant supervision of nurse and physician. This reaction demonstrates to the patient what will happen if he takes alcohol and proves to him that he cannot drink as long as he takes the drug.

After recovery from the reaction the patient is discharged from the hospital and given a supply of tablets and a card to carry. This card identifies him as a patient taking antabus and advises those concerned to notify the hospital in case of a reaction. The relative who helps with the treatment is also carefully instructed. The patient is told to return for a second test on the eighth day. Following the second test, an appointment is given for a psychiatric interview at the office in one week. Maintenance dosage of antabus (from 0.25 to 1 gm. daily) is adjusted to the patient, the amount depending upon the severity of the test reaction and the side-effects. Individual needs determine frequency of subsequent interviews and laboratory tests.

It has been found that individualized personal management enhances the success of treatment and not only avoids dangerous reactions but also overcomes anxiety and keeps up the patient's incentive to carry on.

The following is a preliminary report upon 35 patients referred during a period of six months for alcoholism or its complications. Many were referred by general practitioners or specialists. Some were admitted to the hospital in emergency, and others voluntarily sought treatment. All were private patients and therefore differed in social background and drinking habits from those ordinarily observed in clinics, yet all were very severe chronic alcoholics. All were of middle class background, living in close contact with their families. Although interpersonal relationships had often deteriorated because of the patient's alcoholism, none of them had been completely rejected by his family. No one nationality or religion predominated.

Ten of the 35 patients were admitted with severe complications in addition to chronic alcoholism. Four patients with delirium tremens and one each with acute hallucinosis, polyneuritis, bromide intoxication, arsenic poisoning (suicidal attempt) and cardiac failure were treated by usual clinical methods before evaluation for antabus. In eight cases treatment with antabus was contraindicated—in six primarily for psychiatric reasons, in two primarily because of organic disease. The principal psychiatric contraindication was lack of insight (inability to accept the need of treatment). The organic complications were congestive heart failure in one case and myocardial infarction in the other (see Table 1).

Of the 27 patients who met the criteria for treatment with antabus, 18 were men and nine were women. The age range was 30 to 58, with nine patients in each decade and a median age of 44. Seven had previously taken the conditioned reflex treatment at least once. Several had joined Alcoholics Anonymous. These patients have been followed three to nine months on treatment with antabus. Results were successful (continued cooperation and no return to alcohol) in 16 cases; partially successful (at least one episode of drinking but continued cooperation with treatment) in four cases; and unsuccessful (return to previous drinking habits or organic complications forcing discontinuance of the drug) in seven cases.

TABLE 1.—*Contraindications in 8 of 35 Patients Considered for Treatment with Antabus*

No insight or desire for treatment	3
No insight plus bromide addiction	1
No insight plus cirrhosis of liver	1
No insight plus arsenic poisoning	1
Heart disease	2
Total	8

The following case report is illustrative of successful treatment:

CASE REPORT

The patient, a white male 50 years of age, was admitted with delirium tremens and a history of alcoholism for 20 years. Under intensive treatment the delirium subsided in two days. Results of physical, neurologic, psychiatric, and laboratory examinations were satisfactory. Intensive psychotherapy and antabus were started on the sixth hospital day. Four days later the first test reaction was induced with 90 cc. of wine containing 18 cc. of ethyl alcohol and repeated in 20 minutes. The patient first flushed, then became pale, nauseated and anxious. The severe reaction included rapid fall in blood pressure to 44 mm. of mercury systolic and 0 diastolic, which did not change with oxygen inhalation and intravenous coramine. Sensorium remained clear. Six hours later the patient was completely recovered from the reaction and was discharged from the hospital. On the eighth day of antabus he was given a smaller amount of wine, and the reaction was less severe. Office psychotherapeutic interviews were continued. Drowsiness and lassitude were so severe that it was necessary, after four weeks, to reduce dosage to 0.25 gm. daily. Laboratory work repeated at monthly intervals showed no abnormality. After six months the patient continued to take antabus. He said that he had no desire for liquor and had not tried to drink.

Three of the seven patients for whom the treatment was a failure stopped antabus and returned to old habits, three developed organic complications which led to discontinuance of antabus and one did not cooperate with treatment and subsequently killed herself. With a minimal amount of social work, contact with every patient treated has been maintained. It is felt that success in the continued management depends upon establishment of good relationship with the relatives during the patient's hospitalization and regular personal contact with the patient. In the four cases in which patients returned to old habits, there was lack of family cooperation. That is, the patient had insufficient insight and was unable to maintain treatment, and no one in the family had sufficient control to have him continue taking antabus (see Table 2).

Contraindications to antabus have been outlined by Glud.[5] In the authors' experience the most fre-

TABLE 2.—*Reasons for Failure in Seven Cases*

Lack of cooperation by patient and family	4
Increased retention of sulfobromophthalein with onset of symptoms of liver disease after taking antabus	2
Toxic psychosis beginning three days after starting antabus	1
Total	7

quent organic complications have been cardiac and hepatic diseases.

Of four patients with heart disease, two who had electrocardiographic evidence of severe cardiac damage were rejected; two with minimal damage were treated with extreme caution, and in one of them the electrocardiograms taken during the test reaction indicated alarming increase in coronary insufficiency. Even in patients without cardiac disease, a fall in systolic blood pressure to below 70 mm. of mercury was observed. Hence the authors agree with other observers that disease of the cardiovascular system makes treatment dangerous.

As to liver disease, Voegtlin and co-workers,[11] comparing 17 liver function tests, found that the sulfobromophthalein test best indicates liver damage associated with chronic alcoholism. Although Glud[5] recommended that sulfobromophthalein retention in excess of 15 per cent should contraindicate antabus, the authors have not found this criterion entirely satisfactory. Problems involving liver function were encountered in eight cases. In one of these there were also psychiatric contraindications and antabus was not given. Two patients, treated for liver disease until function was improved, were then given antabus. One tolerated the drug but organic psychotic reaction developed rapidly in the other; it subsided after antabus was discontinued. Another patient with 30 per cent retention of sulfobromophthalein, who was first given antabus by his family physician against the advice of the authors, tolerated the drug well. That patient is included among those for whom successful outcome is reported in this series. Decreased liver function developed in four patients taking antabus: In the two without symptoms antabus was continued; in the other two it was discontinued because of toxic hepatitis and gastrointestinal dysfunction, respectively, with subsequent remissions.

So far, psychiatric factors more frequently than somatic disorders contraindicate treatment. If the patient entirely lacks understanding of his illness and his need for treatment, he will not take antabus. In the belief that the treatment must be entirely voluntary, six patients who did not recognize that alcohol was a problem for them were rejected. One of them was hospitalized primarily for treatment of bromide intoxication.

Until the status of this treatment is established, all danger involved in the test reaction should be carefully studied. As has been noted, alarming fall in blood pressure during a severe reaction is a frequent occurrence. Oxygen, although recommended, has little effect; nor has ephedrine or nikethamide been satisfactory. Ascorbic acid, recently recommended by Bowman,[1] has likewise failed in the authors' limited experience with it. These serious complications make absolutely necessary the constant attendance of doctor and nurse to recognize and combat them before they develop fully. As an added precaution, to prevent dangerous reactions, the amount of alcohol originally recommended for the test reaction has been substantially reduced and the rate of ingestion retarded.

In this series, direct side-effects of antabus were more common than was reported by Jacobsen.[8] Every patient complained of lassitude, often to the extent of interference with normal living. In some instances benzedrine (5 mg.) has proved effective in combating this lethargy, which is usually directly proportional to dosage. Dizziness, interference with taste, and impotence have been frequent. In some cases these effects have been so severe that the antabus dose was reduced to a level not therapeutically effective. A report by Edwards[3] that antabus alone partially inhibits cellular respiration offers a possible explanation of the side-effects.

The authors have found the induction of physiological antagonism to alcohol to be the most successful way of keeping the patients sober and thus permitting maintenance of psychotherapeutic contact with them. However, because of the hazards previously mentioned, antabus is not safe enough to permit general use of it as an antagonist until there is further research on safeguards, and further clinical experience.

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The Use of Antabus in the Therapy of Alcoholic Patients

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SUMMARY

Preliminary studies on the effects of antabus (tetraethylthiuram disulfide) in the therapy of alcoholic patients indicate that it is very valuable in providing a "chemical foundation" for sobriety, even in those with a severe, long term drinking problem. In the first 30 patients treated, a favorable degree of control of the alcoholism has been effected in approximately 80 per cent. When taken regularly the drug maintains in the patient a very high degree of sensitivity to alcohol, quickly producing a number of very distressing bodily reactions whenever even very small amounts of spirits are ingested. Because of its potential dangers, antabus should be used only after thorough clinical and laboratory studies in properly staffed institutions. It is contraindicated in individuals with existing major psychosis or drug addiction and must be used only with caution in patients with diabetes mellitus, cardiovascular disease, goiter, pregnancy, epilepsy, asthma, and hepatic disease. Antabus therapy should be considered only one aspect of the total treatment program for the alcoholic patient.

PERHAPS the greatest difficulty in the treatment of the alcoholic patient is that often he will not remain sober long enough to undergo any real therapy. Some authorities have therefore stated that a minimum of six months to one year of hospitalization is required to lay a foundation before allowing the patient to return to his usual environs and continue treatment. Others have used conditioned reflex (aversion) therapy, first with apomorphine and later with emetine, with varying degrees of success; but this method depends on the after-effects of a short period of conditioning.

About two years ago in Denmark two physicians discovered more or less accidentally that tetraethylthiuram disulfide, or antabus, when ingested prior to drinking would chemically sensitize the individual against alcohol.[2] Since then over 10,000 problem drinkers have been treated with this drug in this country and abroad, under pretty carefully controlled conditions for the most part.[1, 3, 4]

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Antabuse® was supplied through the courtesy of Ayerst, McKenna and Harrison, Ltd., New York.

Presented by the Section on Psychiatry and Neurology at the 79th Annual Meeting of the California Medical Association, April 30-May 3, 1950, San Diego.

INDICATIONS

Since in almost every alcoholic a combination of pharmacodynamic and psychodynamic factors is encountered, no single therapeutic approach is usually effective, but instead a comprehensive program is required. However, it can now be stated that the antabus regimen offers a pretty good "insurance policy" for sobriety in the majority of these patients. Therefore, the author has been using it in almost every case except where the alcoholism is relatively mild or is strictly secondary to a well-defined psychiatric disorder that necessitates primary attention. For example, a person using alcohol mostly in reaction to some acute situational stress might not require antabus, at least as a long-term program.

Of course, the interest in antabus on the part of the public as well as physicians has been rather thoroughly aroused. The manufacturers of the drug reportedly have been receiving 500 inquiries a month about it. The idea of overcoming a very expensive, disabling disorder like alcoholism "by taking a few pills" has fired the imagination of many a worried relative as well as that of many unhappy victims of the condition. Unfortunately, a little reflection makes evident that it is not nearly so simple as that, for the use of the drug is only one component of the therapeutic program.

CONTRAINDICATIONS

For the most part, these are relative rather than absolute. Two deaths have been reported in Europe in patients treated with antabus and suffering from diabetes mellitus, but other diabetics have been successfully treated without complications. Since in the alcohol reaction the cardiac rate and the cardiac output increase, the drug must be used cautiously in patients with cardiovascular disease. Opinion varies as to the use of antabus in patients with considerable liver damage, but the author has treated several such patients without incident, although care was taken to employ proper supportive measures of a nutritional and biochemical sort. Pregnancy has been considered a contraindication, although it is reported that a few gravid women have been successfully managed on the program, and at present the author is treating one in about the fifth month.

Perhaps the two most important conditions interfering with antabus therapy are psychiatric in nature—namely, drug addiction and definite psychosis. In the former case, the patient might take more and more of the habituating drug when deprived of alcohol; in the latter, the patient might use antabus for suicide or otherwise misuse the drug.

Asthma, nephritis, goiter, and epilepsy are other conditions which indicate a cautious approach to antabus therapy.

PRELIMINARY STUDIES

First of all, the alcoholic patient must have, of course, careful physical and neuropsychiatric examination. The author also employs comprehensive laboratory and biochemical studies. In addition to routine tests like blood cell count and urinalysis, serum calcium, phosphorus, glucose, cholesterol total and cholesterol esters, iodine, and bicarbonate levels are determined. A battery of tests are used to investigate liver function thoroughly: Cephalin flocculation, thymol turbidity, albumin-globulin ratio, serum alkaline phosphatase, serum bilirubin level, and sulfobromophthalein excretion rate. Blood acetaldehyde is measured before and after alcohol test reactions, since this is the constituent most affected by antabus and the one presumed to be most important in the sensitization mechanism. Electrocardiographic and electroencephalographic studies are carried out.

PROCEDURE

The alcoholic must be detoxified thoroughly and must be completely off alcohol for at least 48 hours prior to starting antabus medication. Usually he then is given three tablets within 24 hours and about 12 hours later two ounces of spirits is given to test the reaction. If the reaction is very slight, it is sometimes advisable to give an additional two ounces of spirits in one hour. Antabus is continued (one 0.5 gm. tablet at bedtime) and two additional reaction tests are ordinarily given at 48-hour intervals, using progressively smaller test doses of alcohol.

In a satisfactory reaction test, the patient usually shows a heavy flush within ten minutes after ingestion of 1 ounce of spirits, followed by heart-pounding, a feeling of constriction in the chest and throat, and often nausea, headache, and dizziness. The odor of acetaldehyde is almost always easily detectable. After one-half to one hour the patient often drops off to sleep.

It is important to emphasize the virtual necessity of the patient's experiencing two to three full-fledged reactions to alcohol under controlled conditions after being sensitized by intake of the drug. For him to learn about the reaction from hearing about it or even from seeing other patients experience it is usually not sufficient; he must actually undergo the process and in that way imprint the effects on the "feeling levels" of his own nervous system. After an adequate, or "Grade III," response, many an alcoholic verbally expresses a heartfelt aversion to spirits that surpasses any effects produced by conditional reflex therapy with emetine. More important than the psychological effect, perhaps, is the alteration in the pharmacodynamic factor, so that the patient often manifests a true indifference to alcohol even after returning to his usual environs.

Once the patient has experienced a satisfactory response, it is frequently feasible for him to return home with a limited supply of antabus and continue on an out-patient basis. He must continue to take the prescribed dose daily, under supervision by a member of his family if possible. So far the only relapses observed have occurred when the patient consciously or unconsciously neglected to take antabus for several days running. Then, since unbeknownst to him some antabus effect still remained, he often has given himself a painful surprise, becoming quite sick for 24 to 48 hours after ingesting several drinks. Usually by that time the patient is more than willing to return to the hospital and get back on the program.

CORRELATED THERAPY

Having given the patient a chemical foundation for abstinence, the other clinical problems that are usually found in the problem drinker must be dealt with. These are covered by psychiatric care as indicated, including group therapy; by nutritional and endocrine rehabilitation; and by appropriate efforts at social readjustment through counseling of the family and of the employer by the physician or psychiatric social worker.[5] It should be stressed that for most alcoholics antabus is not a therapy in itself but rather a valuable gateway to more fundamental treatment.

The need for appropriate psychotherapy along with medication in the case of the majority of problem drinkers has been emphasized by most of the workers in this line of research, including the Danish physicians who pioneered it. In the first place the alcoholic requires guidance and reorientation in his whole life program. Many alcoholics have profound emotional tensions which have been partly masked by alcoholism and which become in some ways even more disturbing when they are on the sobriety program. Although 40 per cent of problem drinkers are estimated to function pretty well through abstinence alone, the remaining 60 per cent show well defined neuroses or other psychopathologic conditions requiring therapy. In the case of the latter group, to supply antabus without correlated psychiatric treatment would be to treat only one symptom and to ignore the basic problems of the individual.

By the same token, the majority of the problem drinkers show a variety of physical ailments associated with alcoholism. In addition to the well-known anatomical disturbances like gross hepatic cirrhosis and polyneuropathy, more subtle nutritional and biochemical deviations are assuming greater and greater importance as techniques of investigation improve.[6] For instance, many patients have low glucose tolerance and a tendency toward hypoglycemia,[7] apparently on the basis of hypofunction of the adrenal cortex. This disturbance of course is associated clinically with symptoms like "jitters," tension, and fatigue—commonly blamed by some individuals for their inability to remain sober. In others unpleasant physical symptoms like tiredness and tension are associated with low blood iodine, high serum calcium, disturbance in the calcium-phosphorus ratio of the serum, and an elevated serum cholesterol—all associated with diminished thyroid function. In many patients, vague gastro-

intestinal complaints are found to be related to milder forms of hepatic dysfunction, reflected in low serum cholesterol, high serum alkaline phosphatase and serum bilirubin, increased cephalin flocculation and thymol turbidity, and the like. Obviously, such patients require intensive nutritional rehabilitation along with the antabus program.

EVALUATION OF RESULTS

It is too early to appraise the long-term effects of antabus, but initial results in a series of approximately 30 patients give much basis for cautious optimism. To illustrate, several patients with 15 to 25 years of chronic alcoholism and numerous prior hospitalizations with only very transient benefit are maintaining sobriety with antabus and making an adequate social and occupational adjustment with the help of correlated therapies. Many of these patients probably will have to continue this "insurance policy" for a long time to come, just as the diabetic must often continue insulin daily. In the series here under review, the therapeutic results thus far with antabus and correlated therapy have been substantially favorable in approximately 80 per cent of cases.

It is necessary, however, to sound a note of caution. Antabus should be considered a two-edged sword, since the drug is potentially toxic and improperly used might be disastrous. A long-suffering wife, for instance, might put a few tablets into the coffee of her bibulous spouse. Hardly less dangerous would be indiscriminate prescription by physicians without adequate clinical and laboratory investigation beforehand. At present it would seem essential to limit use of the drug to properly staffed institutions, where, of course, both in-patient and out-patient treatment might be undertaken.

ANALYSIS OF THERAPEUTIC FAILURES

About 20 per cent of the patients in this series have not been able to maintain sobriety for a significant period. In each case, of course, the patient quit taking antabus. This points up one of the chief paradoxes in the problem of alcoholics—namely the strong (but largely unconscious) wish to fail or relapse coexisting with the often desperate, conscious desire to overcome the illness. Naturally, this same conflict is present in other psychiatric conditions but rarely to the intense degree found in the average problem drinker. This unconscious drive to disaster has been variously explained. Freud formulated an elaborate if not easily credible theory about a "death instinct." Karl Menninger has written extensively along these lines, referring especially to the "chronic suicide" of the alcoholic. Taking a somewhat different point of view, Bergler has emphasized the role of super-ego tension and the compulsion for self-punishment. From his own observations the author inclines toward the theory that the alcoholic constantly is unconsciously striving to recapture the infantile feeling of omnipotence. Closely related is his "chaos drive," or the need to smash everything to pieces, overwhelm and engulf his environment — much as the infant sends his blocks flying in all directions. The alcoholic is notorious for his inability to follow a regular program, especially one involving self-discipline. Under the pressure of responsibilities in the adult world he has strong drives to "kick over the traces" and smash everything up, including himself. This phenomenon seems to account for the apparent lack of capacity of some of the patients in this series to take a little white pill daily, even though failure to do so jeopardizes everything they consciously hold dear. To combat this aspect of the problem in this group of patients intensive deep-level psychotherapy, supplemented by special accessory techniques, seems to offer the best hope of amelioration. Of course, each time the alcoholic suffers a painful relapse, a certain amount of the reality principle may be driven home to him.

ILLUSTRATIVE CASES

CASE 1: A 54-year-old accountant was admitted to the Sierra Madre Lodge on December 28, 1949, in a heavily intoxicated condition. After detoxification with insulin, intravenous fluids, and endocrine support, thorough clinical evaluation revealed an underlying psychoneurotic tension state of severe degree along with moderate nutritional depletion. Life history revealed an overconscientious, obsessively worrisome and insecure person who had always overextended himself in his occupation to secure approval. Chronic gastrointestinal complaints of 35 years' standing seemed primarily related to a mixture of anxiety and suppressed resentment. Alcohol had been taken in progressively greater quantities during the past 20 years for sedation and escape, until a well-established secondary addiction had developed. The patient began to lose time from work, sporadically had a few days' treatment in "sobering up" sanitaria, and finally was dismissed from his job despite an otherwise excellent work record.

After proper study, this patient was started on antabus and correlated psychiatric therapy, in which sodium pentothal narcoanalysis was particularly effective. Within eight days after admission he had improved sufficiently to leave the hospital and continue on an out-patient basis. He has remained sober to date, takes antabus regularly, and claims no desire to drink. Perhaps more hopeful is the pronounced reduction in emotional tension and associated gastrointestinal disturbances. The patient secured a better job in a bank after the bank president convinced himself of the kind of rehabilitation this patient seems to have embarked on.

It is believed that for good long-term results, the patient will have to continue antabus for a minimum of two years, with periodic psychiatric interviews and occasional narcotherapy.

CASE 2: A 37-year-old professional man began the antabus program in September 1949. He was considered a primary addict of severe degree, having been a problem drinker since first touching alcohol at age 15. The history included several arrests for drunkenness and between 40 and 50 periods of hospitalization in a dozen sanitaria. No therapy seemed to have made any real impression, including office psychotherapy, the Alcoholics Anonymous program, emetine aversion therapy on four occasions, and the combined entreaties and exhortations of friends and relatives. Accordingly, the patient begged for antabus and reacted so thoroughly to the third alcohol reaction test that he acquired a very healthy fear of its effects, in contrast to the transient impression of emetine.

After graduating to out-patient status in one week, the patient did well for about the next three months. He was strongly urged to have comprehensive follow-up treatment, in the way of reeducative psychotherapy and nutritional correction. He cooperated at first but pleaded increasing difficulty in keeping appointments because of the pressure of business. A few days before Christmas the patient's wife reported he was drinking again. A few hours later the patient himself made an appeal to be readmitted to the sanitarium, averring that he was sicker than he had ever been in his life. After he had been rescued, he related that he had not taken antabus for seven days (missing the first two days "unconsciously" and the remainder intentionally) and had expected to "celebrate the holidays with a little drinking before returning to the program." However, he still retained enough antabus sensitization to cause profound reaction so that there was not even temporary enjoyment in drinking. Since that brief escapade the patient has had his business partner administer the prescribed medication to him daily and has remained entirely abstinent and regularly at work. To his friends and associates this sobriety borders on the miraculous, but to his physicians the basic emotional immaturity of the patient and the related tensions severely interfere with his functioning anywhere near his potential capacities. Later, when more receptive, this patient will require more psychiatric therapy, and in the meantime his "chaos drive" is apt to disrupt an already unstable equilibrium. On the other hand, each day that he remains sober on antabus is that much on the credit side of the ledger from many standpoints and should not be lightly dismissed.

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Discussion by NICHOLAS A. BERCEL, M.D., *Los Angeles*

Since the psyche is a public domain, the psychiatric specialist is confronted by laymen's opinions to a much greater degree than let us say a surgeon, whose province is not open to public inquiry. It is for this reason that psychiatrists had to take a considerable amount of public beating because even though they have hammered into the public mind monotonously that alcoholic patients need psychotherapy, their record of success, let us face it, was a poor one. Many psychiatrists went even as far as to surrender the alcoholic case material into the hands of laymen's organizations, which did not help in promoting public confidence in the efficacy of psychological treatment in general. Chief reason for this abyss existing between theory and practice is that the alcoholic patient is like a castle surrounded by a moat over which, up to recently, no bridge could carry us. The best conceived therapeutic program was of no avail as long as the patient was inaccessible, as long as we could not keep him sober between two visits.

The treatments based on antagonism or aversion to which antabus therapy has been added of late, perform the function of the bridge. Alcoholics are now within our reach. As the speaker so carefully emphasized, however, antabus is only one part in an integrated strategy of total push.

The available clinical evidence can be accepted with justifiable optimism. At first glance, the practice of relying on the alcoholic for taking his daily tablet seems to be a handicap. The temptation of not taking the tablet appears to be too great. On second analysis, however, the active part that the alcoholic patient has to take every day in his salvation program represents a daily renewed insurance policy, just as there are people who while unable to lay aside a fraction of their income *every month*, by putting pennies *every morning* in a "piggy bank" succeed in saving up a fortune.

Another advantage of antabus seems to lie in the fact that if an alcoholic is tempted to "beat" the untoward effect of antabus therapy by ingesting a whopping dose of alcohol he is likely to pass out before he has a chance to ponder over the success of his endeavor. Learning from bad experience is not necessarily a bad teacher. The most appealing feature of antabus therapy, however, is its psychological soundness and the opportunity that it offers to study the biochemistry of alcohol metabolism in the body.

I think the speaker deserves our congratulations for lifting our spirits and for the restraint with which he tried to keep this lift within bounds.

A Survey of the Results of Treatment of Gastric Cancer in San Francisco

JOHN L. WILSON, M.D., *San Francisco*

SUMMARY

A survey was made of all patients treated for gastric cancer on the clinic services of the Stanford University Hospital during the 30-year period 1919 to 1948. During the last decade of the survey there were impressive gains in the surgical treatment of this disease. It was possible from 1944 to 1948 to do a gastric resection on half the patients seen with cancer of the stomach. Also, there was a pronounced decrease in resection mortality so that from 1939 to 1948 the mortality rate for subtotal gastrectomy for cancer was 3 per cent.

The over-all five-year survival rate was discouragingly low—4.6 per cent. On the other hand, 23 per cent of those surviving gastric resection lived for five years.

A survey of the management of carcinoma of the stomach from 1939 to 1948 was made in 11 general hospitals in San Francisco. A wide range of resectability and resection mortality rates was observed. The cases from these hospitals were combined with those from Stanford for the same period to form a composite group of 1,128 patients. Analysis of this group of cases from 12 representative hospitals in San Francisco showed encouraging trends toward higher resectability rates with a lower resection mortality.

GREATER success in the treatment of gastric carcinoma depends upon earlier diagnosis and more effective surgical excision. The difficulties of early diagnosis are well known and will not be discussed here. Most laymen and many physicians are overly pessimistic regarding the hazards of operation for gastric cancer. If it can be shown that surgical methods have been greatly improved in recent years, it should be well worthwhile and may even prove influential in bringing more cases to early operation.

This study will present, first, the changing picture of surgical treatment of gastric cancer over the 30-year period from 1919 to 1948 as exemplified by the experience on the clinical service at Stanford University Hospital. Second, since it is believed that a truer picture of the present management of gastric cancer in the community as a whole can be so obtained, the operability, resectability and resection mortality rates in 11 other San Francisco hospitals for the last decade (1939 to 1948) of the above period have been determined.

From the Department of Surgery, Stanford University Medical School, San Francisco.

Presented before the Section on General Surgery at the 79th Annual Meeting of the California Medical Association, April 30-May 3, 1950, San Diego.

OBSERVATIONS AT STANFORD

Every effort will be made to present the data obtained from these surveys in such a way that they may be readily compared with those reported from other sources. The comprehensive studies of gastric carcinoma by Livingston and Pack[3] and by Walters, Gray and Priestley[8] have established a pattern which will be followed.

Source of the Material. The clinical material studied consists of all cases of gastric carcinoma (310 patients) admitted to the clinic services of the Stanford University Hospital during the 30-year period from 1919 to 1948. This group of 310 patients is the basis for the following estimates of operability, resectability and resection mortality rates.

Operability. Operability rates in gastric cancer are in general a reflection of the stage of the disease

TABLE 1.—*Summary of Treatment of Gastric Cancer at Stanford 1919 to 1948, Inclusive*

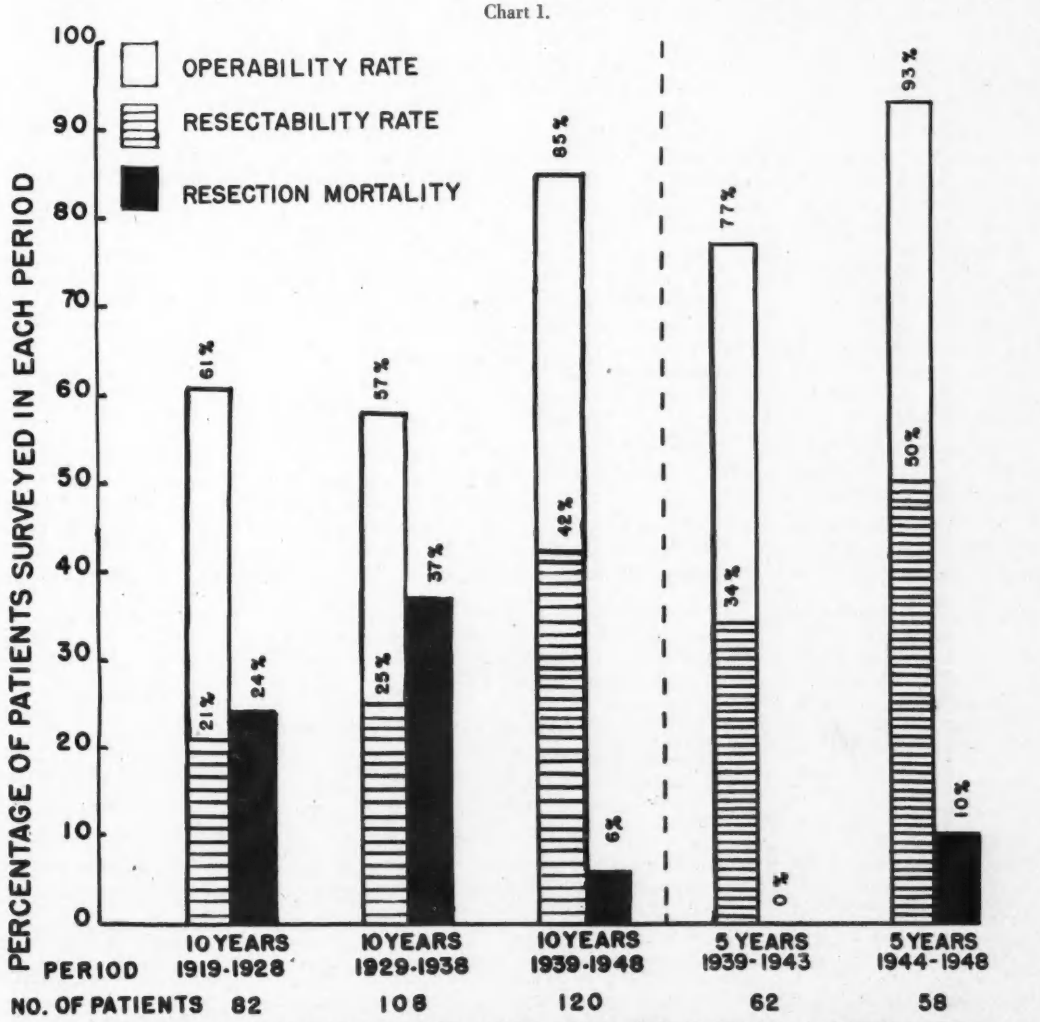
	1919-1928	1929-1938	1939-1948
Number of cases	82	108	120
Number of patients operated upon	48	62	102
Laparotomy only:			
Number of cases	19	21	32
Per cent of total cases	23%	19%	27%
Operative mortality	5%	9%	16%
Palliative procedures:			
Gastroenterostomy:			
Number of cases	12	13	17
Per cent of total cases	17%	12%	14%
Operative mortality	0%	23%	12%
Gastrostomy:			
Number of cases	0	1	3
Per cent of total cases	..	1%	2%
Operative mortality	..	0%	67%
Resections:			
Subtotal resections:			
Number of cases	17	27	38
Per cent of total cases	21%	25%	32%
Operative mortality	24%	37%	3%
Resections of cardia:			
Number of cases	0	0	8
Per cent of total cases	..	..	7%
Operative mortality	..	..	25%
Total resections:			
Number of cases	0	0	4
Per cent of total cases	..	..	3%
Operative mortality	..	..	0%
Operability rate	61%	57%	85%
Resectability rate	21%	25%	42%
Resection mortality rate (for resections of all types)	24%	37%	6%

at the time of diagnosis, but an aggressive surgical attitude is also an important factor in bringing more patients to operation. Operability rates remained relatively the same for the first two decades of the 30-year period but there was a pronounced trend toward higher operability rates between 1939 and 1948. Operability rates by decades from 1919 to 1948 were 61 per cent, 57 per cent and 85 per cent. In the last five years of the survey the operability rate reached the high level of 93 per cent (Table 1 and Chart 1).

Exploratory and Palliative Operations. Table 1 gives the incidence of exploratory and palliative operations by decades. Follow-up studies showed that patients with inoperable carcinoma of the stomach had an average survival of less than two months after discharge from the hospital. For those patients who had only laparotomy the average period of survival was less than three months. For those having a palliative procedure the average duration of life was less than seven months. Partial gastrectomy was not used as a palliative procedure in this series of cases.

Resections. During the first two decades of this study all resections were subtotal gastrectomies of the distal stomach. In the third decade, 1939 to 1948, there were 38 subtotal gastrectomies, eight resections of the cardiac portion of the stomach and

Chart 1.



OPERABILITY, RESECTABILITY AND RESECTION MORTALITY IN GASTRIC CARCINOMA AT STANFORD 1919–1948

LAST 2 COLUMNS, DIVISION OF LAST DECADE OF SURVEY INTO TWO 5-YEAR PERIODS

four total gastrectomies. The resectability rates (based on all cases observed) by decades were 21 per cent, 25 per cent and 42 per cent. During the last five years of the 30-year period, 50 per cent of the patients observed with carcinoma of the stomach had gastric resection (Chart 1).

Resection Mortality. As has been the experience reported from other clinics, there has been a sharp decline in resection mortality in recent years. During the first two decades of this survey the resection mortalities were 24 per cent and 37 per cent. In the third decade (1939 to 1948), however, there were 50 resections of all types with only three deaths, a resection mortality of 6 per cent. Two of the three deaths occurred after resections of the cardia and only one (due to mesenteric thrombosis) followed subtotal gastrectomy.

In the 30-year period there were 94 resections for gastric carcinoma with 17 deaths. The causes of these 17 post-resection deaths are listed in Table 2 by decades. Peritonitis was the commonest cause of death, but in this series there was no death from peritonitis after 1937. The sharp decline in the mortality rate for gastric resection is the result of many factors which are almost impossible to evaluate individually. Improved pre- and postoperative management, based on a better understanding of the physiological disturbances in the surgical patient, has helped make resection safer. Antibiotics and frequent whole blood transfusions are powerful supportive measures now frequently used. Finally, it is noteworthy that records of patients operated upon in the last decade of the survey period show disappearance of post-resection peritonitis and intestinal obstruction, complications related in large measure to operative technique.

It was suggested by Wangensteen and co-workers[6] that use of the aseptic technique in gastric resection was in part responsible for the improved mortality statistics in the University of Minnesota Hospital. Holman[1] also stressed the importance of aseptic gastric resection for carcinoma and has described the technical steps of this procedure as done at Stanford. Twenty-seven of the 50 resections done for gastric cancer at Stanford during the decade 1939 to 1948 were aseptic in type. The pronounced reduction in post-resection mortality was coincident with the frequent use of the closed resection technique, but the record for open resections during this decade also improved. Declining mortality rates for subtotal gastrectomy have been reported from clinics which employ the open technique of resection almost exclusively.[5, 9] It probably matters little whether the resection is open or aseptic in type as long as it is carefully done in accordance with sound surgical principles.

The operability, resectability and resection mortality rates here reported are more easily evaluated when they are compared with similar percentages from other institutions listed in Table 3. Statistics for earlier periods may be found in the surveys of Livingston and Pack[3] and Maimon and Palmer.[4]

Survival Rates. It was possible to obtain complete follow-up information on 297 patients or 96 per cent of the original group of 310. It is the group of 297 completely followed patients which serves as the basis for the estimation of survival rates.

The three, five and ten-year survival rates, based on all cases followed, were respectively 8.5 per cent, 4.6 per cent and 1.1 per cent (Chart 2). Table 4 lists for comparison the survival rates reported by several investigators.

The location of the lesion in the stomach of the 20 Stanford patients surviving more than three years is shown in Figure 1. All except one of these lesions was in the distal half of the stomach. This is due to the fact that during the first 25 years of this 30-year survey only lesions in the distal portion

TABLE 2.—*Causes of 17 Postresection Deaths at Stanford, 1919 to 1948*

First Decade—1919-1928		Second Decade—1929-1938		Third Decade—1939-1948	
Cause of Death	No. Deaths	Cause of Death	No. Deaths	Cause of Death	No. Deaths
Peritonitis	4	Peritonitis	4	Empyema	1
		Intestinal obstruction	3	Mesenteric thrombosis	1
		Pulmonary complications	1	Cause undetermined	1
		Shock	1		
		Cause undetermined	1		
Total deaths	4		10		3

TABLE 3.—*Operability, Resectability and Resection Mortality Rates for Gastric Cancer in Various Hospitals*

Hospital	Period	No. Cases	Operability Rate	Resectability Rate	Resection Mortality: Subtotal Gastrectomy	Resection Mortality: Total and Gastric Cardia Resections
Mass. General Hospital*[9]	1937-1946	832	76%	50%	11%†	27%
Univ. of Minn. Hospital[6]	1936-1945	586	76%	52%	15.2%†	30%
Memorial Hosp., New York[5]	1936-1945	683	79%	35%	12.2%†	30%
Stanford Univ. Hospital	1939-1948	120	85%	42%	3%	17%

* Calculations made from authors' statistics.

† In these hospitals partial gastrectomy was used frequently as a palliative measure. This accounts for poorer risks and higher mortalities.

of the stomach were considered resectable. Carcinoma of the cardia and fundus can now be safely resected and future reviews from Stanford may show an increasing number of long-term survivors of lesions involving the proximal half of the stomach.

A more hopeful and, some contend, more realistic estimate of the value of surgical treatment can be obtained by determining survival rates in the group of patients who survive resection. At Stanford, the three, five and ten-year survival rates of patients surviving resection of a gastric carcinoma were 35 per cent, 23 per cent and 8 per cent (Chart 3). In Table 5 are listed for comparison the percentages of five-year survivors after resection as reported elsewhere.

If, in the future, gastric resection can be done on half the patients seen at Stanford with cancer of the stomach and if, as in the past, at least one-fifth of those surviving resection live five years, then the over-all five-year survival rate should rise from 4.6 per cent to about 10 per cent. This simple calculation suggests that it may be possible with present methods of treatment to double the percentage of five-year survivors of gastric carcinoma.

The series of cases reported here is comparatively small and the percentages quoted are based on too few cases to have great weight. However, there is no question that these studies clearly demonstrate the same encouraging trends toward more and safer resections of gastric cancer which are being reported from other clinics.

TABLE 4.—*Survival Rates in Gastric Cancer*

Source	Period	Survive 3 yrs.	5 yrs.	10 yrs.
Livingston and Pack[3]	1881-1931	3.2%	1.9%	0.7%
Mass. General Hospital[4]	1937-1941	....	7 %	....
Univ. of Minnesota Hosp.[6]	1936-1943	10.7%	6.6%	....
Stanford University Hosp.	1919-1945	8.5%	4.6%	1.1%

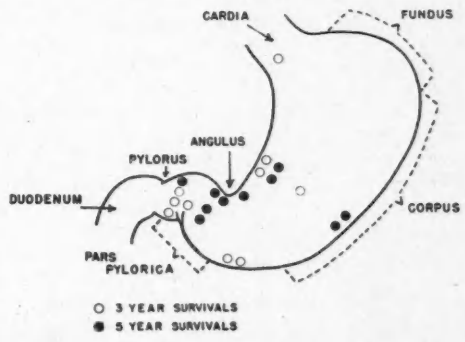
SURVEY TREATMENT OF GASTRIC CANCER IN ELEVEN SAN FRANCISCO HOSPITALS

The various university hospitals and special clinics throughout the world make periodic reports on their management of carcinoma of the stomach. From their data it is possible to draw conclusions as to the results of treatment in these specific institutions that are, in fact, the pilot plants in which new concepts and techniques of treatment are de-

TABLE 5.—*Survival Rates in Patients Surviving Resection of Gastric Cancer*

Source	Survive 3 yrs.	5 yrs.	10 yrs.
Livingston and Pack[3]	29.1%	18.9%	10.7%
Univ. of Minnesota Hospital[6]	29.4%	21.5%	....
Memorial Hospital, New York[5]	....	34.7%	....
Stanford University Hospital	35 %	23 %	8 %

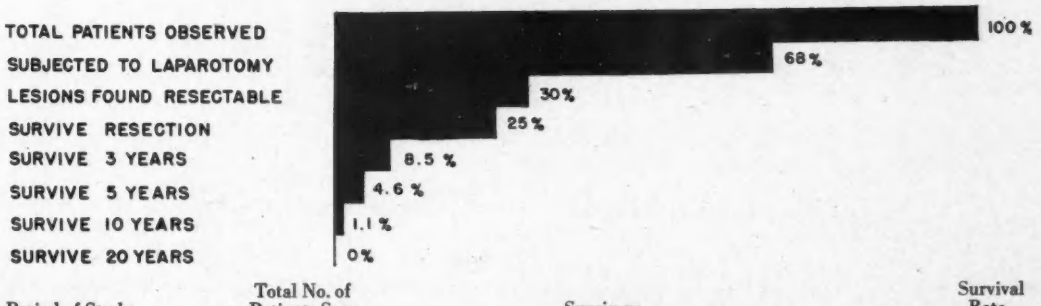
Figure 1.



LOCATION OF LESION IN PATIENTS SURVIVING 3 AND 5 YEARS

Chart 2.

SURVIVAL RATES OF PATIENTS TREATED FOR GASTRIC CARCINOMA AT STANFORD

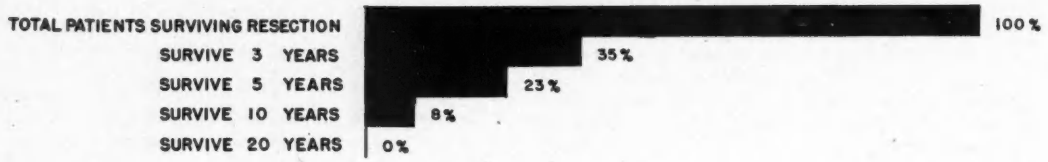


Period of Study	Total No. of Patients Seen	Survivors	Survival Rate
1919 – 1945	258	22 patients survived 3 years*	8.5 per cent
1919 – 1943	237	11 patients survived 5 years	4.6 per cent
1919 – 1938	176	2 patients survived 10 years	1.1 per cent

*Twenty of these patients had gastric resection. The other two patients had gastric cancer proved by laparotomy, were considered not resectable, but lived 3 7/12 and 3 11/12 years after operation before dying of carcinoma of the stomach.

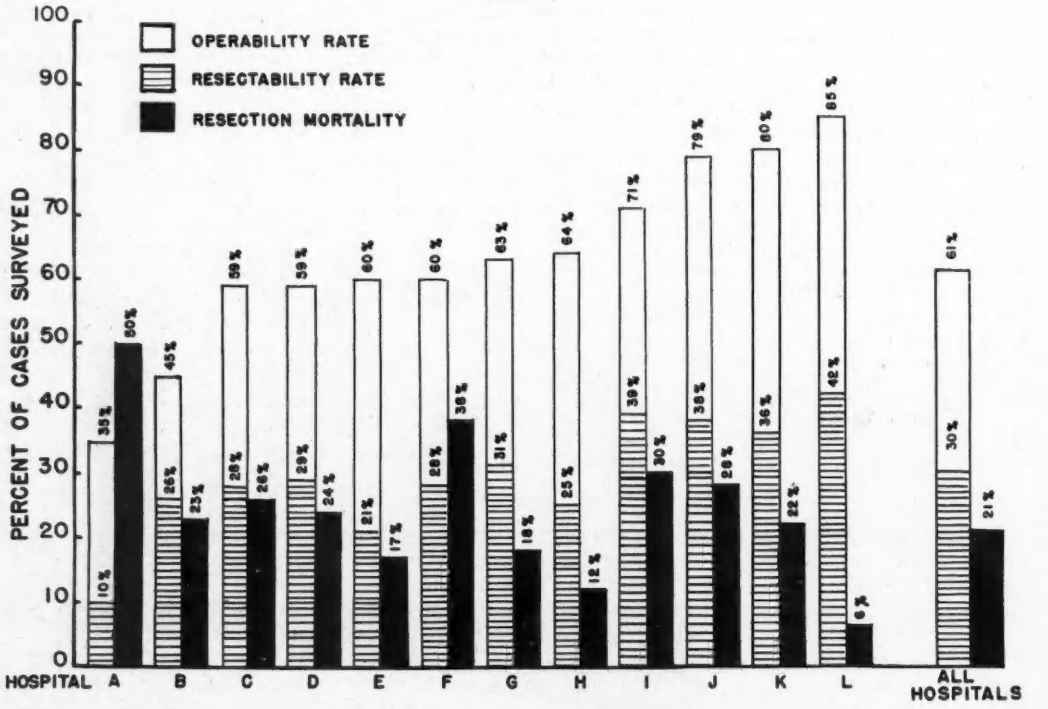
Chart 3.

SURVIVAL RATES OF PATIENTS SURVIVING RESECTION OF GASTRIC CARCINOMA AT STANFORD



Period of Study	Total No. Patients Surviving Resection	Survivors	Survival Rate
1919 – 1945	58	20 patients lived 3 years after resection	35 per cent
1919 – 1943	47	11 patients lived 5 years after resection	23 per cent
1919 – 1938	26	2 patients lived 10 years after resection	8 per cent
1919 – 1928	11	No patients lived 20 years after resection	0 per cent

Chart 4.



OPERABILITY, RESECTABILITY AND RESECTION MORTALITY RATES IN 12 SAN FRANCISCO HOSPITALS, 1939 - 1948

L = STANFORD HOSPITAL

ALL HOSPITALS
1128 CASES
705 OPERATIONS
338 RESECTIONS
72 DEATHS AFTER RESECTION, ALL TYPES

veloped. It is to be expected that for many reasons there will be a certain lag in the acceptance and application of these changing attitudes and methods in the general hospitals of the community. Thorstad[7] called attention to the importance of considering the results obtained in these general hospitals when seeking a true picture of the treatment of gastric cancer throughout the country. Accordingly, he reported the resectability rate for gastric cancer in the Harper Hospital, Detroit, from 1928 to 1942 to be 19.4 per cent and the resection mortality to be 64.7 per cent. For the same period the Detroit Receiving Hospital had a resectability rate of 9.8 per cent and a resection mortality of 57 per cent. These

results were considerably less satisfactory than those reported from many special centers for the same period and served to emphasize his point that such local surveys are useful in obtaining a candid view of the prospects of the average patient with gastric cancer.

It was in the interest, then, of getting a broader and more realistic idea of the management of gastric carcinoma in the community as a whole that a survey was made in 11 of the general hospitals of San Francisco for the ten-year period 1939 to 1948. The staffs of the following San Francisco hospitals made available the data on their cases of gastric carcinoma:

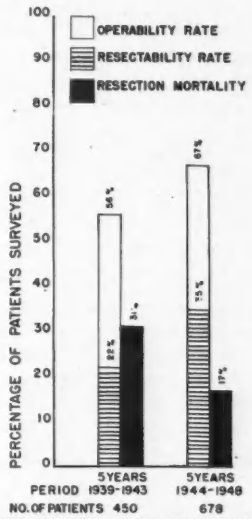
Hospital	Beds[2]
Children's Hospital (for women and children)	250
Franklin Hospital	250
French Hospital	225
Mary's Help Hospital	172
Mount Zion Hospital	163
St. Francis Hospital	300
St. Joseph's Hospital	238
St. Mary's Hospital	371
San Francisco Hospital*	1,336
Southern Pacific Hospital	450
U. S. Veterans' Hospital, San Francisco	396

The results of this survey are summarized in Chart 4. In the 11 general hospitals surveyed the operability rates ranged from 35 per cent to 80 per cent. Resectability rates varied from 10 per cent to 39 per cent and the mortality for resections of all types varied from 12 per cent to 50 per cent. In these 11 hospitals 26 total gastrectomies were done with nine deaths, a mortality of 35 per cent.

It is not the purpose here to compare the management of gastric cancer in the general hospitals of the community with that on a university service. Instead, the primary interest has been in gathering together data on a large series of cases treated in a wide variety of hospitals and by numerous different surgeons in the same city. An analysis of such a series of cases will then give some insight into the status of the management of carcinoma of the stomach in the community as a whole. For this reason the cases treated in the 11 hospitals listed and on the clinic service at Stanford from 1939 to 1948 have been combined. A composite group of 1,128 cases of gastric carcinoma treated in 12 representative San Francisco hospitals was thus formed. In this group there were 425 inoperable and 705 operable cases with 338 resections and 72 post-resection deaths. For the decade 1939 to 1948 the over-all operability rate was 61 per cent, resectability rate 30 per cent and mortality for resections of all types 21 per cent (Chart 4).

There was a definite trend toward better resectability and resection mortality rates in the segment of the community surveyed. In order to show this trend the decade 1939 to 1948 was divided into two five-year periods as shown in Chart 5. It was found that the over-all resectability rate increased by more than one-third (from 22 per cent to 35 per cent) and the mortality for resections of all types was almost halved (reduced from 31 per cent to 17 per cent). These findings suggest that the outlook in the San Francisco community for the average patient with gastric cancer materially improved during the decade of the study. Literally dozens of different surgeons working in a dozen different hospitals in San Francisco have in recent years been able to achieve resectability and resection mortality rates which compare favorably with those reported from certain recognized medical centers (Table 3).

Chart 5.



MANAGEMENT OF GASTRIC CANCER IN 12 SAN FRANCISCO HOSPITALS IN 2 CONSECUTIVE 5-YEAR PERIODS

*The survey of the San Francisco Hospital was made possible by the cooperation of the San Francisco Department of Public Health and covers only the period from 1942 to 1948, inclusive. The Department of Surgery of the University of California Medical School very kindly permitted the inclusion of the cases from their services in this study.

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Carcinoma of the Esophagus and Gastric Cardia

With Special Reference to Treatment

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SUMMARY

During the last five years the thoracic and abdominothoracic approaches in esophageal and gastric surgery have become established. With improvements in surgical and anesthetic technique mortality rates have declined. Preoperative and postoperative care are of great importance.

ONE of the most significant advances in surgery during the last decade is the transthoracic approach to lesions of the esophagus and gastric cardia.

The importance of this advance is apparent in the light of an estimate* that in 1946 5,869 persons had carcinoma at the esophageal and gastric cardia levels—lesions which, by previous clinical and roentgenologic standards, would have been classified as "inoperable." Thus, by a fortunate combination of advances in the fields of anesthesia, surgery, and preoperative and postoperative therapy, plus the availability of antibiotics, carcinoma at all levels of the esophagus and an additional estimated 10 per cent of carcinomas of the stomach now are accessible to surgical treatment. The significance of this advance is apparent when it is recalled that esophageal cancer is more common than cancer of the central nervous system, lip, tongue, mouth, pharynx, duodenum, larynx, thyroid, pleura and peritoneum, kidney, testes, and bone.

ANATOMY

In previous reports,[10, 11] it has been pointed out that investigators are not in agreement regarding the gross anatomy of the gastric cardia. This springs from the fact that the cardia is a physiologic sphincter rather than a gross anatomic structure. Histologically the cardia is a zone about five millimeters in width situated at the esophageal orifice of the stomach. It is lined by columnar epithelium containing mucous glands which resemble those of the pylorus. The significant distinction is that the mucous membrane of all portions of the stomach including the cardia is of the glandular type whereas the mucous lining of the esophagus is of the squamous epithelial variety. It is important that this distinction be made at the outset because significant pathologic and clinical implications will be discussed later in this presentation.

Despite these anatomic differences, malignant conditions existing in the gastric cardia and the distal esophagus present the same surgical problem. Because these structures are anatomically contiguous, the symptoms, diagnostic procedures and therapeutic approach are identical.

PATHOLOGY

The histopathologic characteristics and the mode of spread of malignant lesions arising in the esophagus are quite different from those of lesions originating in the cardia. Thus, carcinoma originating in the esophagus is of the squamous cell variety owing to the squamous type of epithelium from which it originates. Since the mucosa of the gastric cardia is of the glandular type, carcinoma which originates in this region is of the corresponding adenocarcinomatous variety. Adenocarcinoma of the stomach tends to spread to the esophagus by direct extension through the submucosal layer. Squamous cell carcinoma of the esophagus, on the contrary, spreads to the stomach by direct invasion on the one hand and by way of lymphatics to the paracardial lymph nodes on the other. An exception to these pathologic distinctions is the theoretic if not the practical possibility of the origin of adenocarcinoma from rests of gastric mucosa situated in the distal esophagus.

SYMPTOMS AND DIAGNOSIS

In cases of carcinoma of the esophagus and cardia the early symptoms usually are mild. In fact the patient, and too frequently the physician, assumes erroneously that they originate from functional or benign disturbance of the gastrointestinal, respiratory or circulatory system. Dysphagia is the earliest and usually the most important symptom. It is the result of obstruction to the passage of food or fluid through the esophagus and into the stomach. In the beginning it commonly is mild and transitory but usually it recurs or persists. Eventually regurgitation supervenes to relieve the dysphagia or obstruction. The patient's first visit to the physician often is deferred until this time.

Pain may be present but it is not usual. It usually develops late and as the result of infection or extension of the growth. In rare instances bleeding is the first symptom noted. When the patient presents

*Based on U. S. Public Health Service Vital Statistics.[12]

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himself early, alertness to the grave possibilities of mild symptoms is entirely the responsibility of the physician.

In the late stages, the most characteristic feature is progressive loss of weight. At this stage starvation usually causes pronounced lowering of the general morale.

Since many of the problems of surgical treatment of lesions at this level have been solved, the most important responsibility which devolves upon the family physician is diagnosis. In the author's experience, the most common error results from the acceptance of a negative report from one investigative procedure without utilizing other of the various diagnostic methods. Often this may be traced to economic considerations, additional diagnostic procedures being omitted in order to conserve the patient's funds. Another feature not to be overlooked is that in an age of specialization the limitations inherent in all special diagnostic procedures are not generally recognized. In many instances it is only by the combined use of fluoroscopy, esophagoscopy, gastroscopy and biopsy that these diagnostic problems can be solved.

The diagnosis of carcinoma may be made on the basis of a history of dysphagia with roentgenologic and/or endoscopic confirmation. While fluoroscopy usually is of the utmost value, it occasionally happens that the lesion escapes roentgenologic detection. In these instances diagnostic esophagoscopy or gastroscopy or both must be utilized. In cases in which close questioning reveals that the dysphagia is persistent or recurring and is associated with obstruction or a sense of delay retrosternally, diagnostic esophagoscopy is obligatory even though results of fluoroscopy are negative. (It is important, however, to keep in mind the possibility that the symptoms may be produced by suprasternal tension of so-called globus hystericus.) Positive biopsy furnishes valuable and final proof of malignancy.

SURGICAL APPROACH

The solution by surgical means of the problem of carcinoma occurring at the distal esophagus or gastric cardia has been accomplished through the expedient of the transthoracic approach, an outgrowth of the abdominothoracic attack on lesions primary in the gastric corpus, cardia and terminal esophagus. In fact, Phemister's[8] first successful single-stage esophagogastrectomy in 1938 was suggested by Ohsawa's[5] successful abdominothoracic operation five years previously. The value of the combined approach has been emphasized by Garlock[3] who enumerates several advantages: (1) Operability may be determined through a small upper left rectus incision before extending the incision to the thorax; (2) in no other way, prior to opening the thorax, may the surgeon determine the presence or absence of hepatic metastasis, fixation of the growth, the presence of peritoneal implants or extensive retroperitoneal involvement as, for example, the important area about the celiac axis.

The success of these new approaches is the result of a combination of important advances in anesthesiology, thoracic surgery, the care of the undernourished patient, the application of antibiotics and the understanding and handling of pulmonary and cardiovascular complications. The extensive exposure of the esophagus and proximal stomach not only permits surgical removal of lesions of the esophagus and proximal stomach but provides an opportunity for removal of involved lymph nodes and contiguous structures. In lesions of the stomach the new approaches permit choice between total gastrectomy on the one hand and, on the other, resection of the proximal stomach combined with the appropriate esophagojejunal or esophagogastric anastomosis. With respect to lesions of the esophagus, the newer approaches replace the Torek and other procedures wherein external restoration of gastrointestinal continuity is required.

PREPARATION OF THE PATIENT

It is important, when possible, to apply surgical treatment early, before loss of weight, anemia and malnutrition have progressed so far as to require prolonged periods for correction. If operation has been delayed, malnutrition and dehydration must be corrected by the administration of amino acids, glucose and electrolytes. Correction of severe hypoproteinemia may require prolonged delay. In such instances a choice must be made between this delay and operation before the depleted condition is entirely overcome. Anemia must be corrected by the administration of whole blood and appropriate doses of iron and liver extract. Vitamins B and C should be given for several days prior to operation. During the 24 hours before operation, massive doses of penicillin and streptomycin should be administered parenterally and 0.5 gm. of streptomycin given by mouth. The entire thorax and axilla must be prepared for operation and a Levin tube inserted as far as possible before the patient goes to surgery.

ANESTHESIA

The judicious use of the anesthetic agents and adjuvants currently available is indispensable to the successful conduct of open chest operations on the alimentary tract.

TECHNIQUE OF OPERATION

Whereas the history of the technique of operation has been published by Bird,[1] Ochsner and DeBakey,[4] and by Pack and McNeer,[6] Garlock[3] and Sweet[9] have contributed most to the standardization of technique. The author has pointed out elsewhere[11] that a feature of operation equal in importance to the transthoracic approach is the advancement of the stomach or jejunum into the thorax in order to complete gastrointestinal continuity. An addendum is applicable to that report: As early as 1895, Biondi performed transthoracic esophagogastrostomy on dogs through a "buttonhole" in the diaphragm. Apparently, therefore, he was first to advance the stomach into the thorax experimentally. In 1904, Mikulicz, operating upon a dog, advanced

the stomach into the thorax and the animal was in good health six weeks after operation. In August 1938, Cattell "reduced" the stomach into the thorax transperitoneally as a preliminary to subsequent successful transthoracic cardio-esophagectomy.

The essentials of the operation are thoracotomy or abdominothoracotomy with radical excision of a segment of the esophagus, of the proximal stomach, or both, or total gastrectomy with removal of the regional lymph nodes and restoration of continuity by esophagogastric or esophagojejunal anastomosis within the thorax or within the base of the neck.

Following is a brief outline of the technique of operation as utilized in cases reported later in this presentation. In the transthoracic approach the chest is opened, usually through the eighth rib bed. In high-lying lesions the chest may be entered either at the level of the fourth rib or exposure facilitated by division of the seventh, sixth, fifth and as high as the fourth rib. Pleural adhesions, if present, are divided and the left thorax is explored. The judicious use of curare has eliminated the necessity of avulsion, division or crushing of the phrenic nerve in order to overcome its resistance of or the transmission of abdominal tension through the diaphragm. Through an incision in the posterior mediastinum, the distal esophagus is explored manually and involvement of mediastinal lymph nodes noted. The distal esophagus then is mobilized over a Penrose drain.

Some indication of the extent of intra-abdominal involvement may be obtained by palpation through the relaxed diaphragm. Usually, however, it is necessary to incise the dome of the diaphragm. This permits manual exploration of the regional lymph nodes, the liver and the peritoneal surfaces. Should non-resectability be apparent, the operation may be concluded by closure of the diaphragm, the mediastinum and the thoracic cage. If resection of the lesion appears possible, the upper abdominal and left thoracic regions are converted into a single cavity by extending the diaphragmatic incision in either direction as well as through the esophageal hiatus. Resection of the primary lesion with the regional lymph nodes then is carried out with due consideration of the gastric and esophageal blood supply. After the incision in the distal retained portion of the stomach is closed, that organ is advanced into the thorax where end-of-the-esophagus to side-of-the-stomach anastomosis is completed by use of three layers of interrupted silk sutures. The stomach is fixed to the mediastinal and parietal pleura so that it becomes a thoracic organ permanently in whole or in part. The incision in the diaphragm then is closed by suturing it loosely to the stomach wall so as to avoid constriction. In this way the symptoms characteristic of esophageal hiatal hernia are avoided.

When total gastrectomy is required, the esophagus is anastomosed to a loop of jejunum which has been advanced into the thorax. Jejunojejunostomy should be added.

The abdominothoracic approach is extremely valuable for lesions situated primarily in the corpus but with involvement of the cardia and with extension to lymph nodes or other organs below or above the diaphragm. Operability is determined by means of a preliminary incision through the outer margin of the left rectus abdominis. This permits systemic palpation of the stomach, liver, suprapyloric, supragastric, paracardial, pancreaticolienal, middle colic and infrapyloric lymph nodes. Thus the presence or absence of hepatic nodules, peritoneal implants and lymphatic involvement may be determined. If resectability appears to be possible, the preliminary incision is extended upward to and through the costal arch, whence it is extended laterally between the eighth and ninth ribs as far as the posteromedial border of the scapula. The diaphragm then is incised through the esophageal hiatus. From this point on, the procedure may be carried out as described above, with several advantages: (1) Direct visibility for the conduct of all steps of the procedure; (2) accessibility of the celiac axis for more easy ligation of the left gastric artery and removal of the involved lymph nodes; (3) greater ease of resectability of involved adjacent organs such as the spleen, tail of the pancreas, colon or liver; (4) in case total gastrectomy is necessary, visualization of the jejunal blood supply is more satisfactory.

After closing the incision in the diaphragm and approximating the divided costal cartilage with absorbable or non-absorbable suture material, closure of the abdominal and thoracic incisions is carried out in the usual manner.

POSTOPERATIVE CARE

Of importance equal to the careful execution of surgical technique is efficient postoperative care. To the surgeon who is accustomed to operating within the abdomen, the thoracic approach presents peculiar postoperative problems.

The anesthetist has certain responsibilities in the early postoperative period. He should aspirate the tracheobronchial tree before the patient leaves the operating room. He must assure himself that the patient's color is good and the blood pressure is satisfactory. Preferably this is accomplished by proper maintenance throughout the operation. Otherwise the intravenous administration of fluid or blood after the patient has been returned to his room may be required. Intranasal oxygen may be necessary for 24 hours or more to maintain normal color. Carbogen administered by mask is helpful in securing the patient's cooperation with deep breathing. The patient should be turned from side to side at half-hourly intervals and six to eight deep inspirations should be taken at intervals of one hour. In order to encourage deep inspiration and coughing, analgesic drugs should be given sparingly. A high degree of judgment must be exercised in the administration of postoperative analgesics so that coughing is not inhibited by pain. At present the author uses meperidine hydrochloride, 50 to 100 mg. ad-

ministered at four- to six-hour intervals, the amount depending on the age, weight and tolerance of the patient. Experienced special nursing is a distinct asset in the conduct of postoperative care in these cases.

Intrathoracic negative pressure by means of a large intrathoracic Foley inflatable catheter is maintained until drainage through it ceases after two or three days. If this is done, postoperative aspiration of pleural effusion by needle seldom becomes necessary. Auscultation of the chest should be carried out at six-hour intervals during the first few days. Persistence of diminished breath sounds usually is indicative of pulmonary atelectasis well in advance of the usual appearance of increased pulse rate and temperature. In case of atelectasis, or if there is doubt, tracheobronchial aspiration is carried out and repeated if necessary until aeration is adequate in all portions of the thorax.

Nutrition is maintained parenterally for three or four days while Levin suction is in use, and sips of water are permitted. After removal of the tube, liquid, soft and finally solid foods are permitted as tolerated by the patient. Early ambulation is practiced if the functional capacity of the heart allows. Under this program the patient usually walks about the room, is on a general diet and is allowed home by the eighth postoperative day. At this point the exceedingly important follow-up period begins and continues over a period of months. During this time the surgeon should anticipate the patient's problems and sympathetically attempt to minimize them. The maintenance of the morale of patients who have been operated upon for cancer is extremely important during the follow-up period.

RESECTABILITY AND MORTALITY

Two factors affect resectability more than anything else: (1) the time at which the patient consults the surgeon, and (2) the degree of extension of metastasis to adjacent lymph nodes. Resectability increases with the degree of experience of the operating surgeon. During the early period of development of these operations as well as in the early experience of individual surgeons, the operative mortality was high. Between 1871 and 1907, mortality was 100 per cent. Between 1933 and 1943, the mortality experienced by all surgeons active in the development of these procedures ranged from 23 to 75 per cent. Reports[2, 7, 9, 11] from a variety of sources in 1948 indicate a mortality of from zero to 57 per cent.

Outline reports of ten recent consecutive cases are given in Table 1. Included is a variety of benign and malignant lesions in order to represent the possibilities of this type of surgical approach and therapy. The patient who died had malignant disease.

CASE REPORT

A typical case is that of a Caucasian woman, aged 70 years, first observed October 23, 1948. The principal complaint was of gas-like pain, present since May, which appeared to encroach on the capacity of the stomach. There was inappetence, inability to eat more than a little at a time and recent pain in the lower sternal region, left subcostal margin and to the back. Loss of 20 pounds in body weight was reported.

At the time of examination the body weight was 113½ pounds. The pyloric portion of the stomach was palpable. Lymph nodes were not enlarged. A recent roentgenogram disclosed a defect of the mid-stomach extending to within 2 cm. of the cardia. There was no roentgenologic evidence of metastasis. Upon gastroscopic examination, pallor of the

TABLE 1.—*Series of Ten Cases in Which Operation Was Done for Relief of Lesions of the Esophagus or Gastric Cardia.*

Case No.	Age	Diagnosis	Operation	Results
1	54	Adenocarcinoma of corpus with extension to cardia.	Transthoracic cardioesophagectomy.	Died 11th day postoperative of bronchopneumonia.
2	42	Adenocarcinoma of corpus with extension to cardia.	Transthoracic cardioesophagectomy.	Living 24 months postoperative with evidence of generalized carcinomatosis.
3.	69	Large benign peptic ulcer of esophagus.	Transthoracic esophagocardiectomy.	Living and well 22 months postoperative.
4	47	Squamous carcinoma of esophagus with adenocarcinoma of cardia.	Transthoracic esophagocardiectomy.	Survived for eight months after operation.
5	58	Squamous carcinoma mid-esophagus.	Transthoracic esophagocardiectomy.	Working 26 months after operation.
6	51	Adenocarcinoma of corpus with extension to cardia.	Subtotal gastric resection with esophagogastrostomy.	Survived operation. Died two months postoperative of carcinomatosis.
7	57	Leiomyosarcoma of cardia.	Transthoracic local excision of leiomyosarcoma.	Working 18 months after operation.
8	70	Reticulum cell lymphosarcoma of corpus with extension to cardia.	Abdominothoracic total gastrectomy with esophagojejunostomy.	Living and well 20 months after operation.
9	56	Massive ulcerating reticulum cell lymphosarcoma of corpus and cardia.	Abdominothoracic subtotal gastric resection with partial hepatectomy and esophagogastrostomy.	Survived operation. Allowed home on the 14th day postoperative to remain under the care of family physician.
10	44	Intractable cardiospasm; chronic duodenal ulcer.	Transthoracic vagotomy, gastrojejunostomy, cardioplasty and repair of esophageal hiatal hernia.	Living and well two months after operation.

mucosa and the presence of a large mass protruding from the posterior and superior walls on a broad pedicle were noted. Certain areas were covered with a glary white exudate but ulceration was not observed. The gastroscopic impression was sarcoma of the stomach with lymphosarcoma a strong possibility.

Surgical exploration through a Garlock incision on November 16, 1948, confirmed the presence of the mass which appeared to be resectable. Biopsy of a lymph node was reported as indicating lymphosarcoma.

Total gastrectomy was performed, and in addition the spleen and the entire greater omentum were removed. Esophagojejunostomy with jejunojejunostomy was carried out and the openings in the diaphragm and chest and abdominal walls closed. Except for aerophagia, convalescence was uneventful. Since operation the patient has received 2,800 roentgens of radiation over the abdomen. The patient was still living 20 months after operation.

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Gastric Resection

Preoperative and Postoperative Care

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SUMMARY

Perhaps in no other field of surgery does attention to minute detail play so important a role in determining success as it does in gastric operations.

As surgery of the stomach develops toward even greater security and favorable results can be expected with greater confidence, the several aspects of preoperative and postoperative care hitherto regarded as secondary demand closer consideration.

ADEQUATE preparation of the patient who is to undergo a gastric operation requires the utmost attention to minute detail. Not infrequently the recognition and treatment of disturbed bodily physiologic processes occasioned by the gastric lesion are of greater significance than any other preoperative problem.

In many instances gastric disorders are accompanied by recognizable pathologic changes in other systems, notably the cardiovascular-renal system. For this reason, the close cooperation of the internist and the surgeon is of the greatest benefit in securing a successful surgical outcome for the patient. With improvement in technique and care making gastric operation possible in older age groups, the incidence of cardiac difficulties with which a surgeon is confronted has likewise increased. An evaluation of the patient's cardiac status should include an estimate of the ability of the heart to withstand the conditions of stress to be expected during an extensive surgical procedure.

As a general rule, all patients who have reached 50 years of age should have an electrocardiogram preoperatively, whether or not the previous history is suggestive of cardiac disease. The persistent changes caused by previous silent coronary artery occlusions may be observed on the routine tracing. A suggestion of cardiac damage alerts the surgeon for possible postoperative complications.

Cardiac arrhythmia in the postoperative period may be averted by the administration of quinidine for several days before operation. The use of digitalis in some form is, of course, mandatory for the treatment of patients in actual or impending cardiac decompensation. Such appropriate yet simple preoperative measures, designed both to discover and to treat disturbed cardiac function, provide definite contributions toward minimizing postoperative cardiac complications and in obtaining good end results.

The presence of diabetes, if properly controlled, does not add measurably to the risk of operation. Consequently operation is not denied patients whose insulin requirements may be excessively high. However, it is usually necessary to hospitalize them for a few days prior to operation. During this period, the urine may be freed of sugar and ketone bodies by the administration of fluids and insulin. Isotonic saline solution or physiologic 5 per cent glucose solution may be used intravenously. If the latter is used, the 50 gm. of glucose it contains are covered by 25 units of regular insulin (one unit of insulin for each 2 gm. of glucose). The diet in the immediate preoperative period may contain considerably more carbohydrate than is usual for the patient in order to insure a maximum storage of glycogen in the liver. It is perhaps wise to provide not more than 175 gm. of carbohydrate daily, however.

The selection of an anesthetic agent poses an important problem, for the diabetic patient tolerates none of them well. In general, ether anesthesia should be avoided whenever possible, since it produces hyperglycemia. However, when the diabetes is complicated by severe cardiac disease, ether may still be the agent of choice, especially in elderly patients. In recent years, the use of nitrous oxide combined with intravenously administered curare to obtain muscular relaxation has proved of great benefit in the care of such patients. Spinal or even local anesthesia may be applicable in some cases.

Since the time of action of insulin is shortened by both anesthesia and surgical trauma, insulin must be given at more frequent intervals in the immediate postoperative period. Initially the postoperative insulin requirements are best determined by frequent blood sugar determinations; later the qualitative sugar reaction of the urine may provide a reasonably accurate guide. Fluid requirements are met mainly with the administration of saline solution and glucose solution covered by insulin (one unit per 2 gm. of glucose). It must be remembered, however, that since part of the glucose administered parenterally is excreted in the urine, qualitative measurement of the sugar contained in the urine will not always be an accurate guide for the amount of insulin necessary. The problem is oftentimes a

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delicate one, for acidosis and hypoglycemia are at opposite poles of quite a narrow bridge of therapy. In the immediate postoperative period it is wiser to err in providing too little control than too much.

Patients who have hemorrhagic lesions of the stomach and duodenum usually require several whole blood transfusions in addition to the general measures necessary to prepare them for gastric operation. When the hemorrhage has been massive the low hemoglobin level must be raised before operation is undertaken. If, however, the bleeding is of such severity that it becomes impossible to raise the blood count to the desired level, operation is mandatory to control the source of the bleeding.

In many patients with chronic secondary anemia resulting from a gastric lesion, the hemoglobin level may not rise beyond 30 per cent even with repeated transfusions. This is especially true in patients with gastric carcinoma. It is interesting, however, that these patients withstand operation surprisingly well. Although there is some controversy, the authors believe that multiple transfusions are of greater benefit to these patients when administered preoperatively than when given in the convalescent period.

A most important consideration in the preoperative period is the recognition of the effects produced by organic obstruction at or near the gastric outlet. Persistent pyloric obstruction accompanied by vomiting may lead to profound renal disturbances which affect not only the function of the kidney but its histologic appearance as well. Not generally appreciated, however, is the fact that a renal lesion may oftentimes serve to initiate a peptic ulcer.

The renal insufficiency which results from chronic gastric retention is due to the alkalosis that follows extensive loss of blood chlorides from vomiting. The kidneys are able to maintain normal function when they are called upon to excrete urine with pH values ranging from 4.5 to 7.8, even though the pH of the blood remains fairly constant at about pH 7.35. Urine of low pH value is excreted without difficulty, but the kidneys do not tolerate for long excretion of urine with a high pH. Thus, a state of relative or even absolute renal insufficiency may develop if alkalosis is present for a considerable time.

Such a state is manifested by changes in the chemistry of the blood wherein the non-protein-nitrogen is elevated, the CO_2 combining power of the plasma is increased and the concentration of serum chlorides is decreased. The severity of the changes in the chemical values will usually parallel the degree and duration of the obstruction. Also, as is well known, tetany may develop if the alkalosis is not corrected.

It is important to remember that uremia may be decreased by simple parenteral fluid therapy which, by virtue of the large volume of water, washes the solids through the renal system. However, a decrease in the non-protein nitrogen value may not always indicate a corresponding return in actual kidney function. This has been proved by creatinine clearance tests which frequently reveal poor kidney function even though the blood non-protein nitrogen value may have decreased considerably with the administration of parenteral fluids. To attempt gastric operation in the presence of unrecognized renal insufficiency is to invite disaster. It must be remembered, however, that oftentimes poor renal function will not be significantly improved until the primary gastric lesion has been treated surgically. In these instances, the selection of an optimum time for operation based on an accurate appraisal of the patient's general status and an intelligent interpretation of the blood chemistry values is of utmost importance.

The loss of blood chlorides which results from the persistent vomiting of gastric fluid containing a high concentration of hydrochloric acid can be effectively combated by the parenteral administration of normal saline combined with glucose solution. The glycogen reserve of the liver is replenished by the use of glucose solution. Patients who are in actual or borderline cardiac decompensation can be given glucose solutions in a concentration as high as 50 per cent, although 20 to 25 per cent solutions are less liable to cause venous thrombosis. Saline solutions should be isotonic, since with greater concentrations venous thrombosis is liable to occur.

The role of potassium depletion in patients with high intestinal obstruction has recently been a popular subject in the surgical literature. There is no doubt that there is considerable potassium loss from vomiting, more so with duodenal than with gastric lesions. However, it is necessary to make certain of the need for potassium before potassium solutions are administered, for indiscriminate use of them is highly dangerous. It must be remembered that the normal level for serum potassium is 4 to 5 mEq. while the fatal level of serum potassium is only 12 mEq. Not only is the margin of safety slim but the value of potassium, especially in the treatment of the effects of vomiting from pyloric obstruction, is questionable. Should its use be indicated, frequent serum potassium determinations to control the amount administered are absolutely necessary.

For most patients, two to four days of intensive preparation for operation are sufficient, although if dehydration is especially pronounced and the pyloric obstruction is high grade, this period may be slightly prolonged. The stomach is decompressed by an indwelling gastric tube drained by a Wangensteen suction apparatus. Constant suction is rarely used. Instead, the suction is interrupted for two-hour periods three times during the day at regular meal times. The patient is allowed to have clear liquids orally and is encouraged to be ambulatory during these two-hour periods. Frequently the nasogastric tube is removed at bedtime to insure uninterrupted rest and to prevent the development of pulmonary complications.

The gastric enlargement will not be affected to any great extent by the preoperative program of suction. Since the increased size of the stomach

results from chronic work hypertrophy of the gastric musculature, an appreciable change in size could not be expected during the few days of preparation. The amount of edema in the gastric wall seems to be decreased, although frequently this is not pronounced.

The stomach is lavaged extensively with large amounts of tap water the night before and the morning of the operation. There is probably no additional benefit to be derived from the use of dilute solutions of hydrochloric acid. The mechanical cleansing of the gastric lumen to remove all particulate matter is probably the most important factor in the local preparation of the stomach. The production of acid is frequently stimulated by the lavage and aids in the bacterial sterilization of the stomach.

POSTOPERATIVE CARE

Although the principles governing the immediate postoperative care of surgical patients in general are applicable, certain therapeutic measures apply especially to patients who have undergone gastric operation. Continuous gastric suction is maintained for 48 hours after operation so that the duodenal and gastric secretions will not accumulate and distend the gastric remnant. Undue pressure upon the lines of suture may cause slight leaks which lead to intramural or extragastric abscesses. On the morning of the third day, the suction apparatus is clamped off, while the gastric tube is allowed to remain in place. After four hours, the amount of retained secretion in the stomach is determined. If this is found to measure no more than 120 cc., the tube is removed. Should there be larger amounts, it is wise to maintain suction for another day or two. In elderly patients in whom the likelihood of pulmonary complications is considerably increased by the presence of the indwelling gastric tube, removal of it at an earlier time, perhaps in as little as 12 to 24 hours following operation, may be considered.

The use of adequate but not excessive amounts of parenteral fluids is essential. The best guide to fluid therapy will be the determination of the amounts lost by gastric suction and in the urine. Usually three liters of fluid, one of which is saline, will fulfill the daily requirements. It must be remembered that oftentimes the amount of fluid lost through gastric suction is relatively small, indicating that the patient is retaining much of the duodenal and pancreatic secretions through a functioning gastroenterostomy. Under these conditions, one must be careful lest the circulation be impaired by excessive fluid administration. Adequate vitamin intake must be assured from the start. This is best accomplished by the addition of sufficient amounts of vitamins B and C directly to one of the daily intravenous infusions.

Water in 30 cc. amounts is given every hour after the gastric tube has been removed. This is progressively increased to 60 cc. per hour during the morning and to 90 cc. during the afternoon of the fourth day. Clear liquids are offered on the fifth day, followed by a progressive gastroenterostomy diet on the sixth day. By the time of discharge from the hospital, the patient receives a soft diet served in three to five feedings per day depending upon his ability to take the larger or smaller feeding. The patient is encouraged to continue with a soft diet for at least one month, after which he is permitted to add to his diet cautiously until almost a regular diet is being consumed. It is wise to permit the adoption of a liberal diet initially when the reparative processes are at their height rather than to delay for several months the institution of an almost regular diet. It is surprising how many patients do very well with no dietary restrictions. Patients who have undergone partial gastrectomy for nonmalignant disease should not be permitted to use tobacco in any form.

Perhaps the most important single factor in success or failure in the care of patients who have undergone gastric operation is the prevention of pulmonary complications. In the authors' opinion, early and effective ambulation provides the best safeguard against the development of acute pulmonary disease. On the day following operation, the patient is got out of bed at least twice, preferably three times. He is not allowed to sit in a chair but is forced to walk a few steps. A scultetus binder applied to the abdomen will provide a sense of security by virtue of its snug fitting nature. While up and about, the patient is encouraged to breathe deeply and to cough, since this is more effective while he is in the upright position. Should the patient be unable to raise thick sputum, or if the cough is ineffective due to pain, intratracheal suction is a valuable procedure which can be performed on the ward without difficulty. Oftentimes, even if the catheter cannot be inserted into the trachea, the slight irritation produced in the nasopharynx may produce an effective cough.

As a precaution against vascular complications, the nursing staff is not permitted to place pillows beneath the patient's knees in the popliteal spaces. The discomfort of the straight leg position is advantageous, since the patient, continually striving to find a comfortable position, will be forced to move his legs considerably. Also, even the mild compression of the popliteal veins is avoided.

Dicumarol and Quinidine in the Ambulatory Treatment of Chronic Auricular Fibrillation

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SUMMARY

Thirty-three patients with chronic auricular fibrillation were treated with digitalis and quinidine and in addition were given Dicumarol® to reduce the risk of embolism. In 21 of the patients the fibrillation was caused by rheumatic heart disease, and in 12 by arteriosclerosis or hypertension. Normal sinus rhythm was restored in 55 per cent of the 33 patients, in 67 per cent of those with arteriosclerosis or hypertension, and in 45 per cent of those with rheumatic heart disease. Embolism did not occur.

It is well established that the efficiency of a heart with chronic auricular fibrillation is decreased by from 15 to 79 per cent.[7, 10, 20] Reversion to normal rhythm increases cardiac efficiency. The chief objection heretofore to restoration to normal rhythm has been based upon the danger of the formation of emboli. If this danger could be minimized, it is doubtful that anyone could object to an attempt to increase cardiac efficiency by conversion of auricular fibrillation to normal sinus rhythm.

It was the purpose of the study here reported to:

1. Inhibit the formation of thrombi and thereby eliminate the possibility of embolism.

2. Determine the clinical cardiac efficiency of a slowly fibrillating heart after digitalization.

3. Attempt to establish normal sinus rhythm by the use of quinidine.

4. Redetermine the clinical cardiac efficiency after restoration to normal sinus rhythm.

MATERIAL

Thirty-three patients with chronic auricular fibrillation, from the cardiac clinic of the Los Angeles County General Hospital, were studied. There were 29 males, four females. The ages varied from 17 to 83 years. Twenty-one of the patients had rheumatic heart disease, and 12 had arteriosclerotic or hypertensive heart disease. Duration of fibrillation in most cases exceeded two years prior to the study.

METHOD OF STUDY

1. All patients were initially digitalized and were maintained on digitalis during the entire study. After digitalization, clinical cardiac efficiency was estimated on the basis of circulation time, vital capacity and venous pressure.

2. A prothrombin time study was done initially. If the prothrombin time was normal, a daily dose of 100 mg. of Dicumarol® was given for the first three days. On the fourth day the prothrombin time study was repeated. If the therapeutic zone had not been reached, then 100 mg. of Dicumarol was administered daily for the next two days and the prothrombin time then was rechecked. Once a therapeutic level was reached it was found that 100 mg. of Dicumarol given every second day would usually maintain that level from week to week.

The desired therapeutic effect of Dicumarol was to maintain the prothrombin time in a range of from 20 to 40 per cent of normal.

Prothrombin time was determined according to Quick's[17, 18] modification, using a constant temperature block and rabbit brain for the thromboplastic substance (normal prothrombin time 12 to 13 seconds). The thromboplastic substance was made up in small amounts to maintain its freshness.

Prothrombin time was determined daily for short periods to evaluate the relative resistance or susceptibility to the drug and in most cases was checked later at weekly intervals.

3. For purpose of emphasis, the frequently published method of one of the authors[22, 23] for the administration of quinidine is herein repeated.

Method of Giving Quinidine

Day No.	8 a.m. Gm.	10 a.m. Gm.	12 noon Gm.	2 p.m. Gm.
1	0.1	....	....	....
2	0.1	0.1	....	....
3	0.1	0.1	0.1	....
4	0.1	0.1	0.1	0.1
5	0.2	0.2	0.2	....
6	0.2	0.2	0.2	0.2
7	0.33	0.33	0.33	....
8	0.33	0.33	0.33	0.33
9	0.33	0.67	0.67	....
10	0.67	0.67	0.67	....

If the patient complained of any toxic symptoms, such as diarrhea, gastric distress, nausea, etc., the dose was reduced to that of the previous day, for a few days; then the indicated schedule was resumed.

The importance of minimal doses of quinidine during the first few days is stressed to detect possible idiosyncrasy. It should also be stressed that the patients were ambulant; no emergency treatment was necessary, and there was ample time for quinidinization. Previous studies have indicated that if the maximum amounts of quinidine in a 24-hour

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period exceeded 2 gm., the establishment or restoration to normal sinus rhythm could not be adequately maintained on average daily doses.

4. After reversion to normal sinus rhythm resulted, the clinical studies of circulation time, vital capacity and venous pressure were repeated.

Venous pressure was determined by the direct method of Cohen,[5] vital capacity by means of the McKesson apparatus, and circulation times with ether for arm-to-lung and with calcium gluconate for arm-to-tongue.

5. Maintenance doses of Dicumarol, digitalis, and quinidine were continued for periods up to 20 months.

RESULTS

Of 33 patients treated, 18 (55 per cent) were restored to normal sinus rhythm; 15 were not. Of the successfully treated patients ten were in the group with rheumatic heart disease and eight in the group with arteriosclerotic or hypertensive disease. Thus the treatment was successful in 45 per cent of the rheumatic group and in 67 per cent of the arteriosclerotic and hypertensive group. This corroborates a previous report[24] of higher incidence of good response in arteriosclerotic and hypertensive patients than in those with rheumatic heart disease.

Tables 1, 2, and 3 summarize the details in the 33 cases. No embolic phenomena were encountered. One patient in the rheumatic group died suddenly. Postmortem examination revealed acute myocardial infarction due to coronary thrombosis.

The changes in the clinical cardiac efficiency in those cases in which normal rhythm was restored are summarized in Table 4.

The average change was an improvement of 22 per cent. This corroborates reports by others[7, 10, 20]

TABLE 1.—*Rheumatic Heart Disease Restored*

Case No.	Age	Sex	Duration Fibril.	B.P.	Before Treatment: Vit. Cap.	Ven. Pres.	Circ. Time: Ether	Gluc.	After Restoration: Vit. Cap.	Ven. Pres.	Circ. Time: Ether	Gluc.	Remarks
1.	46	F	2 wks.	140/100	2.0	82	7	16	2.4	80	5	13	Restored 2nd day.
2.	38	F	3 yrs.	130/90	2.0	168	10	24	2.6	96	7	18	Full 'Q' routine necessary.
3.	39	M	6 yrs.	124/84	2.0	124	15	30	3.4	142	12	22	Restored on 8th day 'Q.'
4.	33	M	2 yrs. (plus)	155/84	2.4	170	10	35	3.0	102	8	22	Full routine 'Q.'
5.	38	M	7 yrs.	138/86	3.0	160	12	31	3.6	96	8	20	Full 'Q' routine.
6.	66	M	3 yrs.	90/60	1.2	410	11	55	1.2	290	10	40	Amount of 'Q' required unknown.
7.	58	M	3 yrs.	115/90	2.0	74	10	21	2.8	76	7	18	Died at home due to ASHD* with coronary thrombosis. No 'Q' one week prior to death.
8.	61	M	25 yrs.	126/88	1.6	190	14	35	1.6	100	9	22	Known cardiac 45 yrs.; Amount unknown.
9.	49	M	3 mos.	90/78	4.2	136	11	24	4.4	92	7	18	Full dose 'Q' required.
10.	47	M	2 yrs.	150/94	2.6	112	6	14	3.4	102	6	13	Full dose 'Q' required.

*Arteriosclerotic heart disease.

TABLE 2.—*Rheumatic Heart Disease Unrestored*

Case No.	Age	Sex	Duration Fibril.	B.P.	Before Treatment: Vit. Cap.	Ven. Pres.	Circ. Time: Ether	Gluc.	After Treatment: Vit. Cap.	Ven. Pres.	Circ. Time: Ether	Gluc.	Remarks
1.	62	M	2 yrs.	170/84	3.7	124	20	50	4.3	102	15	30	Periods of "flutter" on 'Q.' Dicumarol toxicity—hematuria.
2.	17	M	2 yrs.	120/80	1.6	90	15	32	1.8	86	12	26	Frequent episodes of cong. heart failure and periods of flutter with 'Q.'
3.	48	M	4 yrs.	126/40	2.5	164	10	22	2.2	120	8	18	G.I. upset for 1 wk., followed by hematuria due to Dicumarol.
4.	32	M	1 yr.	180/80	2.6	100	15	45	2.4	92	12	27	Right hemothorax—900 cc. —due to Dicumarol.
5.	68	M	14 mos.	105/80	1.2	140	7	34	1.4	132	6	30	Felt better, less dyspnea—but remained cyanotic.
6.	68	M	1 yr.	146/54	3.6	124	11	35	3.8	112	10	32	Frequent episodes of cong. heart failure.
7.	46	M	6 mos.	100/70	2.2	116	11	20	2.8	104	9	22	Four episodes of cong. heart failure.
8.	29	M	2½ yrs.	120/78	2.7	106	20	32	3.1	102	14	26	Frequent attempts with 'Q' without results.
9.	24	F	1¼ yrs.	100/60	1.5	164	12	34	1.5	166	12	34	Cardiac enlargement grade four.
10.	47	F	2 yrs.	140/80	2.1	156	8	21	2.1	176	8	15	No improvement.
11.	39	M	8 yrs.	135/90	3.0	148	5	19	3.6	102	6	15	Cardiac symptoms since 1931. No cong. heart failure.

that cardiac efficiency is significantly increased by the restoration of a fibrillating heart to normal rhythm.

As long as Dicumarol was administered to maintain a therapeutic zone between 20 and 40 per cent of normal, embolism did not occur in this series.

Most of the patients have been under observation for over one year.

COMMENT

Clinical studies have shown that the cardiac output is increased, on the average, 30 per cent by conversion of slow fibrillation to normal sinus rhythm.[7, 10, 20] Experimentally in animals, Eyster and Swarthout[7] found cardiac output to be decreased by an average of 40 per cent with the onset of auricular fibrillation; Lewis[14] demonstrated a 20 per cent decrease. Thus, a fibrillating heart is in a state of decompensation. Abolition of auricular fibrillation brought about subjective improvement in patients studied.[22, 23, 25]

As long as auricular fibrillation persists there is the risk of the formation of thrombi and subsequent emboli. There has been considerable controversy in the literature* as to whether the restoration of normal rhythm increases the risk. Obviously, the optimum situation would prevail if, regardless of rhythm, the hazard of embolic phenomena were minimal. In recent years the use of 3,3'Methylenebis (4 - hydroxycoumarin), Dicumarol, has been accepted as an effective means of preventing the formation of fresh thrombi if the prothrombin in the blood is maintained at a given level of deficiency.[2, 3, 4, 6] The plan of "Dicumarolization" before and during therapy with quinidine in an attempt to convert chronic auricular fibrillation to normal sinus rhythm is, therefore, logical. The present study has offered such a plan.

It is proposed, on the basis of this series of cases, that the restoration to normal rhythm increases cardiac efficiency (as evidenced by improvement in circulation time, vital capacity and venous pressure); that the maintenance of therapeutically low levels of

*References: 9, 11, 12, 13, 16, 17, 19, 21, 26, 27.

TABLE 3.—*Arteriosclerotic and Hypertensive*

Case No.	Etiol.	Age	Sex	Duration Fibril.	B.P.	Before Treatment: Vit. Cap.	Ven. Pres.	Circ. Time Ether	Circ. Time Gluc.	After Treatment: Vit. Cap.	Ven. Pres.	Circ. Time Ether	Circ. Time Gluc.	Remarks
(A) RESTORED														
1.	ASHD	67	M	3 mos.	110/76	4.0	100	6	14	3.8	76	6	12	Restored after second day 'Q' therapy.
2.	ASHD	75	M	5 mos.	110/74	4.6	108	9	17	4.2	76	5	18	Restored sixth day.
3.	AS-HHD	75	M	2 mos.	200/102	2.1	150	5	22	2.7	46	7	27	Restored fifth day.
4.	ASHD	60	M	1 yr.	140/92	1.4	210	14	32	1.8	144	11	21	Normal on eighth day 'Q.'
5.	AS-HHD	71	M	6 yrs.	185/110	1.3	130	11	40	2.2	44	8	28	Restored on full dose 'Q.'
6.	ASHD	83	M	11 yrs.	120/60	3.4	96	16	37	3.2	92	18	27	Normal on third attempt on fifth day 'Q.'
7.	ASHD	48	M	10 mos.	120/80	3.2	108	7	17	3.6	100	6	15	Normal on seventh day.
8.	HHD	75	M	5 mos.	200/100	3.6	126	6	18	3.8	92	6	16	Restored on fifth day.
(B) UNRESTORED														
1.	AS-HHD	74	M	5 yrs.	140/92	3.8	220	13	25	3.6	180	13	27	Complete heart block. Pulse dropped to 36.
2.	HHD	71	M	6 mos.	184/106	2.4	126	7	33	2.8	106	6	26	Left vent. strain. Marked improvement.
3.	HHD	56	M	3 mos.	200/110	1.4	300	22	37	1.4	300	22	35	Slow pulse (48); No change.
4.	ASHD	82	M	1 yr.	160/78	2.0	74	11	22	2.4	78	8	18	Symptomatic improvement; Pulse 72.

ASHD—Arteriosclerotic Heart Disease
HHD—Hypertensive Heart Disease
AS-HHD—Arteriosclerotic and Hypertensive Heart Disease.

TABLE 4.—*Changes in Clinical Cardiac Efficiency After Restoration of Normal Rhythm.*

	Rheumatic: Average Change	Rheumatic: Per cent Change	Hypertensive and Arteriosclerotic: Average Change	Hypertensive and Arteriosclerotic: Per cent Change
Vital Capacity	540 cc. Increase	23% Increase	213 cc. Increase	7% Increase
Venous Pressure	45 mm. of saline, Decrease	28% Decrease	45 mm. of saline, Decrease	35% Decrease
Circulation Time:				
Calcium Gluconate	2.7 sec. Decrease	25% Decrease	.9 sec. Decrease	10% Decrease
Ether	7.9 sec. Decrease	29% Decrease	4 sec. Decrease	16% Decrease

prothrombin in the blood has minimized the risk of embolic phenomena during and after conversion to normal rhythm.

Recently Foley and Wright[8] proposed long term anticoagulant therapy for chronic auricular fibrillation, thus decreasing the hazard of embolic accidents without attempting to change the cardiac rhythm. Such a plan has apparent advantages; and the authors of this presentation would add to it the attempted conversion to normal sinus rhythm, thereby decreasing by a large percentage the number of patients who would need to be maintained on anticoagulant therapy for an indefinite period of time.

The authors have found, as did Foley and Wright[8] and Olwin[15] that once a therapeutic deficiency of prothrombin in the blood has been reached and stabilized, maintenance may usually be effected without determinations of the prothrombin time any more often than seven to 14 days.

CONCLUSIONS

1. Every attempt should be made to convert chronic auricular fibrillation to normal rhythm. The authors prefer the combined use of digitalis and quinidine.

2. The present and previous studies indicate that the clinical cardiac efficiency of a fibrillating heart with a slow ventricular rate is definitely increased after restoration to normal rhythm.

3. Dicumarolization apparently reduces to a minimum the danger of embolic phenomena during and after conversion of auricular fibrillation to normal rhythm.

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The Administration of Anticoagulants

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SUMMARY

Heparin is administered parenterally. Its therapeutic effect is measured by the clotting time of the whole blood, determined by the method of Lee and White. An excessive anticoagulant effect is controlled by the administration of specific antagonists, toluidine blue or protamine sulfate. Dicumarol* is administered orally in amounts sufficient to reduce the prothrombin activity of the plasma to between 10 and 30 per cent of normal. The prothrombin time, which represents such a reduction in prothrombin activity, will vary according to the method by which the determination is performed, the thromboplastin used, and the technique followed. Excessive prolongation of the prothrombin time is antagonized by the administration of vitamin K in large doses. Long-term therapy with Dicumarol is sufficiently hazardous to require considerable experience on the part of the physician. Where an immediate anticoagulant effect is necessary, yet prolonged administration anticipated, combined therapy with both heparin and Dicumarol may be used until the prothrombin time is prolonged satisfactorily, whereupon heparin may be discontinued.

DESPITE the accumulation of a large body of literature on the use of the anticoagulants and the repeated publication of the details of the administration of these drugs, questions are still raised and cases reported which indicate an incomplete understanding by many physicians of the fundamental principles governing the administration of these drugs. For these reasons it is felt desirable to reiterate in as simple and concise a manner as possible the basic facts concerned in the use of heparin and Dicumarol, presented according to the outline in Table 1.

HEPARIN

Heparin is not effective orally, but it is effective by all routes of parenteral administration. Its action is manifested by the prolongation of the coagulation time of the whole blood and its effect is measured with sufficient accuracy for clinical purposes by the determination of the clotting time of whole blood in a test tube by the method of Lee and White.[9]

The advantages of heparin as an anticoagulant are several. It may be administered by the various parenteral routes: Intravenously (by intermittent injection or by continuous drip); subcutaneously (in aqueous solution or in Pitkin menstruum); or intramuscularly (in concentrated or dilute aqueous solution or suspended in oil or in a gelatin-dextrose medium). Its effect in prolonging the coagulation time of the whole blood is prompt unless it is suspended in a menstruum which delays absorption. Its effect wears off rapidly when the drug is withheld unless it has been administered in a menstruum which releases it slowly. Finally, the effect of heparin on the coagulation time can be determined conveniently at the bedside.

Heparin has two disadvantages clinically. It is expensive and it cannot be administered by mouth.

Intravenous Administration. Heparin is most commonly administered intravenously by the intermittent injection of the sodium salt dissolved in saline diluent in a concentration of 10 mg. per cc.[1, 7, 21] Injections are made at intervals of from three to six hours, most commonly at four-hour intervals. If the preliminary clotting time of the whole blood is normal, 50 mg. of sodium heparin in 5 cc. of saline is injected intravenously and the clotting time is determined at intervals of approximately one hour for the first four hours. The clotting time is usually prolonged from 30 to 60 minutes at the peak of the drug's effectiveness, and it does not return to normal until three to four hours have elapsed. Depending upon the response of the patient to this initial dose, 50 to 75 mg. of heparin is administered intravenously every four hours and the clotting time is determined immediately preceding each subsequent injection. The clotting time should be determined several times during each day of administration until the response of the particular patient is clearly determined.

TABLE 1.—*Administration of the Anticoagulants*

I. *Heparin*
- a. Intravenous, intermittent, or continuous.
- b. Heparin/Pitkin menstruum.
- c. Depo-Heparin.
- d. Aqueous Heparin, dilute, or concentrated.

II. *Dicumarol*
- a. Short-term.
- b. Long-term.

III. *Combined anticoagulant therapy*

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*"Dicumarol" is the registered collective trademark of the Wisconsin Alumni Association which controls the use thereof.

Heparin in saline may also be administered intravenously by continuous drip to bedridden patients.[1, 8] The object is to prolong the clotting time of the blood to from two to four times the normal time and to maintain this prolongation for the duration of therapy. This effect is generally achieved if 300 to 500 mg. of heparin added to a liter of 5 per cent glucose is administered at a rate of 15 to 25 drops per minute for the entire 24 hours. At this rate slightly more than 10 to 15 mg. of heparin is administered per hour and the total amount of saline introduced per 24 hours is about 1,200 cc. If this technique is employed, the clotting time should be determined every two to three hours, since longer intervals without testing are unsafe and have resulted in fatalities.

Heparin in Pitkin Menstruum. Loewe and his associates[10, 11] have advocated the use of heparin given subcutaneously in Pitkin menstruum, with or without the addition of vasoconstrictors (epinephrine and ephedrine). Loewe ordinarily administers an initial dose of 400 mg. of sodium heparin to patients weighing up to 200 pounds and follows it with 300 to 400 mg. given in single injections subcutaneously every other day. Administration is designed to maintain the clotting time between 30 and 60 minutes as determined by the Lee-White method. In the presence of a severe thromboembolic tendency 400 to 500 mg. of heparin in Pitkin menstruum is given and an attempt is made to prolong the clotting time to from one to two hours. Heparin in Pitkin menstruum is excessively painful and patients frequently refuse a second injection. As a further disadvantage, the response of the clotting time of the whole blood to this form of administration has been very irregular and unpredictable. Efforts are being made to produce a more satisfactory menstruum.

Depo-Heparin. Depo-Heparin Sodium® (Upjohn), a preparation of 200 mg. of heparin sodium, with or without vasoconstrictors, per cc. of a gelatin-dextrose medium, appears to be less painful than heparin in Pitkin menstruum, but it acts in a similar manner. There has not been sufficient experience with this product to assess fully its ultimate value. Depo-Heparin appears to be particularly useful as a means of administering heparin during the first few days of combined therapy, before Dicumarol has become fully effective. Two hundred milligrams given intramuscularly twice a day is satisfactory for the majority of patients. The clotting time, determined just before a dose is to be given, should not exceed 20 minutes. If it does, the dose should be postponed for six hours, or omitted.

Aqueous Heparin. Heparin may also be administered intramuscularly, dissolved in aqueous media for prompt absorption or suspended in oil menstruums for delayed absorption. It has been claimed that the administration of heparin in these media is less painful than when Pitkin menstruum is used. Intramuscular injection is to be preferred, not only because it is less painful, but because absorption is more rapid and more regular. While aqueous heparin has ordinarily been used in a concentration of 10 mg. per cc., Stats[20] and Neuhoff[13] have reported the successful use of a concentrated aqueous solution of heparin containing 100 mg. per cc. They administered the preparation in doses of 100 to 200 mg. initially, and either 100 mg. every eight hours or 120 to 140 mg. every 12 hours, depending on the coagulation time determined before each administration. The total daily dose should not exceed 450 mg. No confirmatory reports have come to the author's attention.

Control of Bleeding Due to Heparin. The first step in the control of bleeding due to or aggravated by heparin is to withdraw the drug. Transfusions, preferably of fresh, whole blood may be given to replace the blood lost and to stimulate blood coagulation.

There are two substances which appear to have a specific antagonism to the anticoagulant effect of heparin: The azo dye, toluidine blue,[2] and the protein from fish roe, protamine sulfate.[16, 17] Both promptly restore the coagulation time of the blood to normal; but the effect may be transient, and repeated injections, as indicated by the clotting time of the whole blood, may be necessary over a period of several days. Both drugs may be administered intravenously in doses of from 1 to 4 mg. per kg. of body weight, but a dose of 2 mg. per kg. of body weight, administered intravenously in 250 to 500 cc. of normal saline, appears to be adequate with either drug.

The toxicity of toluidine blue is relatively unknown. Although strongly hemolytic in dogs, it has not produced toxic effects when given in therapeutic doses to man. In man, the urine and stools become highly colored for 36 to 48 hours following the administration of therapeutic doses, but the skin does not become discolored when such doses are used. The experience with toluidine blue is extremely limited.

The protamines neutralize heparin in vitro and in vivo, although they themselves possess anticoagulant properties. Protamine sulfate is a foreign protein, and intravenous injection of it into a dog is followed by serious toxic effects. Apparently the reactions in the dog are anaphylactoid reactions peculiar to the canine species, since they do not occur in other experimental animals and have not occurred in man in the somewhat limited clinical experience so far reported.

DICUMAROL

It is believed that Dicumarol (3,3′ methylenebis-[4-hydroxycumarin]) produces an anticoagulant effect by suppressing the formation of prothrombin in the liver. Its effect is reflected in the prolongation of the prothrombin clotting time of plasma. When administered in ordinary therapeutic doses, it does not prolong the clotting time of the whole blood as determined in glass test tubes by the Lee-White

method. It must be remembered, however, that Dicumarol does produce a prolongation of the coagulation time of the whole blood under certain circumstances. The administration of Dicumarol in amounts sufficient to prolong the prothrombin clotting time of the plasma excessively is reflected in the prolongation of the coagulation time as determined in glass tubes. Also, the coagulation time of the blood is prolonged following the administration of small amounts of Dicumarol when the Lee-White test is performed in siliconel tubes.

Dicumarol has two advantages over heparin. It is cheap and it is effective when administered orally. There is no commercial preparation of Dicumarol for parenteral administration.

Dicumarol has certain disadvantages. When it is administered initially, there is a delay of from 48 to 72 hours in the development of its maximum effect as measured by the prolongation of the prothrombin time. Therefore, when the immediate hazard of embolization is great, heparin should be administered concurrently to protect the patient during this initial latent period. When Dicumarol is discontinued, its effect on the prothrombin time persists for from two to seven days. Therefore, when hemorrhagic complications occur during the administration of Dicumarol, it is necessary to invoke active measures to antagonize the effect of the drug promptly and efficiently.

The response of different individuals to given doses of Dicumarol is not predictable. Furthermore, the response of a single individual to given doses of Dicumarol may vary from day to day. It is necessary, therefore, to determine the prothrombin clotting time of the plasma on each day before Dicumarol is given.

The expense of performing a prothrombin test every day minimizes the economic advantage of Dicumarol, but, when a patient who has been receiving Dicumarol has been under observation for a time, it is frequently possible to lengthen the intervals between tests to as much as one week. However, extending the interval to more than 48 hours should not be attempted unless the physician has had extensive experience with the drug. It is evident that use of such a drug requires painstaking and meticulous observation of the patient and of the laboratory findings during the entire period of anticoagulant therapy.

The laboratory control of Dicumarol therapy must be understood clearly by any physician who wishes to use the drug as an anticoagulant. If the results of the prothrombin test are interpreted cautiously, they serve as an adequate guide to the administration of Dicumarol to the majority of patients. The one-stage method, first described by A. J. Quick and subsequently modified by other investigators, is used ordinarily for clinical purposes.*

The test is performed by adding to a sample of decalcified plasma an excess of ionic calcium and of thromboplastin and then determining the time necessary for the plasma to clot. It is based on the concept that if there is an excess of calcium and of thromboplastin in the coagulation system, the speed of clotting will vary in proportion to the concentration of prothrombin in the plasma. It is recognized that the actual facts are more complex than might be indicated by this simple explanation. The test is used because it provides the best available guide for clinical work, and because, without it, Dicumarol cannot be used either safely or effectively.

The following facts must be considered in the interpretation of the results obtained from the test by any given laboratory. First, there are several modifications in the technique of performing the prothrombin test. Second, there are several thromboplastic substances which can be used. Finally, the test is sufficiently sensitive to variations in technique, concentrations of reagents, and to environmental conditions that, using the same method and the same thromboplastin, significant variations in results may be obtained by different laboratories, or even in the same laboratory from day to day.

The clinician must understand the mechanism of the test and the potential causes for the variations which may be encountered in order to interpret the values reported to him. He must know what method is being used, what thromboplastin is being used, and what values are obtained when the prothrombin time is determined on plasma from normal subjects.

If the technique is varied or if thromboplastin from another source is used, values obtained on normal plasma will differ, sometimes significantly, from values obtained ordinarily. In such instances the standards of reference are no longer accurate for the results obtained on samples of plasma obtained from patients.

Thromboplastins prepared in different laboratories differ in potency, as do various lots of thromboplastin prepared in the same laboratory. Thromboplastin must be stored in a refrigerator at 0° C., but some degree of deterioration may occur despite this precaution. The material must be checked for potency at the time of use.

It is customary for each laboratory performing tests of the prothrombin clotting time to derive what is known as a "prothrombin activity curve." The prothrombin clotting times of undiluted samples of plasma (whole plasma) from normal persons and of similar samples of plasma diluted to 50, 25, 12.5, and 6.25 per cent of normal concentration are determined. The values, in seconds, are plotted against the per cent concentration of the diluted plasma. It is assumed that the reductions in prothrombin activity produced by diluting normal plasma with saline represent roughly the effect of orally administered Dicumarol in prolonging the prothrombin time of a patient's plasma.

* The one-stage method of determining the plasma prothrombin clotting time is described in detail by A. J. Quick; the two-stage method, by W. H. Seegers; and modifications of the one-stage method, by other authors, in the *Transactions First Conference on Blood Clotting and Allied Problems*, Josiah Macy, Jr., Foundation, New York, 1948.

Some workers report their results in per cent of prothrombin activity. Others report prothrombin times directly in seconds. It is the theory behind curves of this type that the temporal values obtained in one laboratory can be compared to those from any other laboratory by converting them into percentage of normal. It has not been demonstrated convincingly that conversion to per cent will permit exact comparison. However, the use of the percentage system permits a satisfactory comparison between the values obtained in various laboratories when there has not been a technical error in performing the test. An error in technique which affects the prothrombin time in seconds will be perpetuated, not corrected, by conversion of the temporal value into per cent of prothrombin activity.

Whether the results of the test are reported directly as the prothrombin time in seconds, or converted to per cent of prothrombin activity, the daily report from the laboratory should always include prothrombin readings in seconds for both the patient and the control. When the report is made in per cent alone, the clinician is completely dependent upon the figure reported and has no opportunity to evaluate the result in terms of the normal standard. It should be clear that, whereas the values in per cent for a given sample of blood in two or more laboratories should be similar, values in seconds will differ according to the method and thromboplastin used.

The routine for administering Dicumarol is as follows:[22]

1. The prothrombin clotting time of the patient's whole plasma is determined each day before the dose of Dicumarol is ordered for that day.

2. On the first day of therapy, if the preliminary prothrombin time is normal, 300 mg. of Dicumarol is administered orally in a single dose.

3. Thereafter, Dicumarol is administered according to the prothrombin time on the particular day, the response of the patient to previous doses, and the trend of the prothrombin curve, whether upward or downward. Ordinarily: (a) If the prothrombin activity is greater than 30 per cent of normal, 100 to 200 mg. of Dicumarol is given. (b) If the prothrombin activity is between 10 and 30 per cent of normal, 50 to 100 mg. of Dicumarol is given. (c) If the prothrombin activity is less than 10 per cent of normal, Dicumarol is withheld.

This scheme is modified frequently according to the trend in the prothrombin activity on the given day. Occasionally, patients will require doses of 200 mg. almost daily to reach and maintain a therapeutic level. Hyperreactors, especially those with liver damage, congestive heart failure, or renal insufficiency, may not require more than 50 mg. a day. It is better to give smaller doses every day than to give massive doses on two to three days out of the week.

The object of therapy is to keep the prothrombin activity between 10 and 30 per cent of normal. This is the equivalent of a prolongation of the prothrombin clotting time to between 30 and 50 seconds *as determined by the Link-Shapiro technique and using thromboplastin prepared from rabbit lung.*

Long-Term Anticoagulant Therapy with Dicumarol. It is not feasible to obtain a daily prothrombin time on patients who need anticoagulant therapy for an indefinite period.[6, 14, 15, 19, 22] Such patients include those with phlebitis migrans, recurrent thrombophlebitis, selected patients with coronary thrombosis and myocardial infarction, and those patients with rheumatic heart disease and auricular fibrillation who periodically release showers of emboli to the peripheral circulation.

Such patients are hospitalized for a few weeks, and Dicumarol therapy is carried out in the conventional manner. When the patient's response is determined, and if his daily requirement is fairly constant, he is sent home on a specified dose of Dicumarol and with instructions to report twice a week for a prothrombin test. If the prothrombin level shows only minor fluctuations, the time interval between prothrombin determinations is extended to a week. Since this method of management is somewhat hazardous, it is important that the patient cooperate intelligently by taking the exact amount of Dicumarol prescribed and appearing regularly for prothrombin determinations.

E. Sterling Nichol of Miami, Florida, has devised a simple, rapid formula for determining whether the patient's plasma prothrombin time represents a satisfactory diminution of the prothrombin activity. A daily control determination must be done on whole plasma obtained from a normal subject. A therapeutically satisfactory prolongation of the plasma prothrombin clotting time on any given day is between two and two and one-half times the control reading for that day, provided that the control value is no longer than 20 seconds. Thus, if the control value is 15 seconds, a satisfactory prolongation of the plasma prothrombin time is between 30 and 37 seconds. If the control value is 20 seconds, the patient's prothrombin time should be between 40 and 50 seconds.

Control of Bleeding Due to Dicumarol. To reduce an excessively prolonged prothrombin clotting time or to stanch bleeding during the administration of Dicumarol, three measures are indicated. The drug should be withheld until the prothrombin time is reduced to a safe level. Temporary shortening of the prothrombin time and decrease in bleeding may be effected by the transfusion of fresh whole blood (may be citrated), or of lyophilized plasma (reconstituted with 0.1 per cent citric acid and distilled water[3]). Finally, vitamin K preparations in doses of 60 to 75 mg. should be injected intravenously, and these injections should be repeated every four hours until the prothrombin time is satisfactorily reduced and remains so.[4, 18] In the occasional patient who does not respond favorably to ordinary vitamin K preparations, the use of vitamin K_1 oxide is sometimes effective.[5, 12] Massive doses of vitamin K and of vitamin K_1 oxide have been given on num-

erous occasions without ill-effect, the total dose in some instances having been within the range of 500 to 1,000 mg.

COMBINED THERAPY WITH HEPARIN AND DICUMAROL

If there is urgent need for immediate anticoagulant effect in a patient for whom Dicumarol therapy is desired, heparin may be administered concurrently with Dicumarol until the prothrombin time has been prolonged sufficiently to insure complete protection to the patient. Heparinization may influence the prothrombin clotting time if the blood used for determining the prothrombin time is taken during the first three hours following the injection of heparin. A specimen for determining the prothrombin time should be taken immediately preceding the injection of the maintenance dose of heparin, usually about four hours after the preceding dose. Ordinarily the coagulation time at this interval is not more than 10 to 15 minutes. When heparin is being given in a menstruum which delays absorption, blood for the prothrombin time should be obtained just before the daily dose of heparin is given. The clotting time of the blood will not be influenced by Dicumarol as long as the prothrombin time is not excessively prolonged and while the clotting time is determined in glass tubes by the method of Lee-White. Ordinarily there is no difficulty in managing the administration of either drug if these points are kept in mind.

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A Simple Electrosurgical Treatment of Rhinophyma

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RHINOPHYMA, the so-called "potato-nose," is a fibrous hyperplasia of the skin of the nose and adjacent cheek regions. It is practically unknown in women and is apparently becoming rarer in men. Contrary to popular belief, it is by no means always the result of alcoholic indulgence, although alcohol exacerbates rosacea, the common precursor of rhinophyma. Treatment is indicated if the condition causes ugly deformity or impairment of breathing.

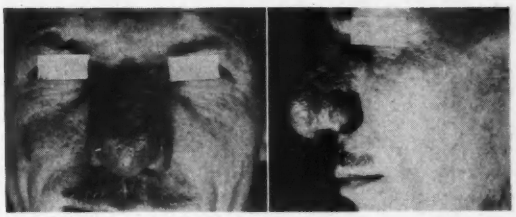

Figure 1.—Typical case of rhinophyma before operation.

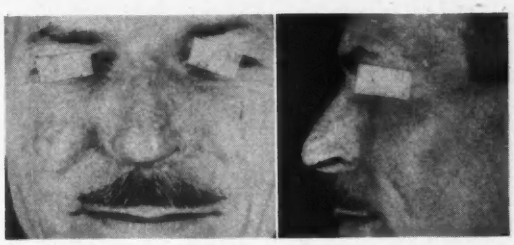

Figure 2.—Same patient as in Figure 1. Final results six months after operation.

PATHOLOGY

Rhinophyma is fibrous hyperplasia of the nasal skin resulting from chronic and recurrent inflammation of the sebaceous glands of the skin. Usually it follows long-continued and intractable rosacea in which recurrent congestion of the superficial capillaries and veins ultimately leads to a sort of vascular fatigue or paresis. Besides the general hyperplasia, there is pronounced dilation of the sebaceous follicles and telangiectases which combine to cause serious distortion of the whole organ.

TREATMENT

The classical treatment of this condition consists of simply shaving down the hypertrophied skin until normal contour is obtained. If the periosteum or perichondrium is not exposed, epithelial regeneration from the sebaceous glands is rapid. An objection to this method is that, owing to the extreme vascularity of the involved skin, there is so much bleeding during operation that accurate sculpturing of the nose is virtually impossible.

This objectionable feature of the operation has been overcome by substituting the electrosurgical knife for the cold knife. The operation is performed in one stage under pentothal anesthesia and the operating time required is 30 minutes or less. Any standard electrosurgical unit with both cutting and coagulating currents may be used. A variety of cutting "tips" should be available. The surgeon should be comfortably seated with easy access and a good view of the patient's entire face. The authors use Physoderm® with dexachlorophene for preoperative antisepsis of the patient's face. Using the cutting current of the electrosurgical unit, the nose is sculptured down to normal contour just as though the work were being done on an inanimate medium. The cutting current seals the smaller capillaries and as the larger vessels are encountered the bleeding is controlled by switching from a cutting to a coagulating current. The electrosurgical cutting tips must be kept free of coagulated tissue by scraping them with a knife. As the nose assumes a more normal contour, smaller points are used to curve the alar and add artistry to the completed job. When the sculpturing has been completed, hemostasis is obtained by coagulation of vessels from which bleeding persists, but care must be used not to destroy tissue. The procedure described is also carried to the involved skin on the cheeks adjacent to the nose.

Postoperatively, the area is treated just as though it were a burn. A bland ointment and a gauze pressure dressing are applied. The external portion of the dressing is changed as it becomes moist. In the second week, areas of sloughing occur. This stage is best handled by alternating wet boric acid or saline compresses with ointment dressings. Healing begins as soon as the sloughed material separates and is generally complete by the fourth or fifth week.

The epithelial covering is at first pink and fragile. It must be protected from sun, wind and direct trauma until the epithelium becomes thickened. toughened and attains normal circulation.

Precautions:

1. Because this is an elective procedure, the patient should be in as good general health as possible. Most of the patients requiring the operation are elderly, and a thorough physical checkup is indicated.
2. The anesthetic must be non-explosive.
3. The excision of tissue must not be carried so deeply that the bone or cartilage is exposed, for then spontaneous epithelialization would not occur

and subsequent skin grafting would be necessary.

4. The excision must not be carried inside the nares lest cicatricial stenosis result. (If an error is made on the conservative side, further touch-up can always be done later.)

5. Infection should be watched for and treated if it occurs. (Infection has not occurred in any of the cases in the author's experience.)

CASE REPORT

A white male, aged 41 years, a salesman, consulted the authors because his prospective clients were so fascinated by his nose that he was failing in his work. There was no history of undue exposure to elements or excessive use of alcohol. General health was good. Rosacea of the nose had been present for four years with progressive development of rhinophyma in the past two years. Six months previously, a series of six x-ray treatments had been given with no appreciable change in the condition.

Physical examination revealed the typical rhinophyma shown in Figure 1. There were no other pathological findings.

Operation was performed as previously described in this presentation and the patient left the hospital the following day.

Sloughing of the area occurred but the sloughed material had completely separated by the eighth postoperative day and healing was rapid. The patient returned to work 26 days after operation and has remained entirely well for more than three years.

The final result, six months postoperatively, is shown in Figure 2.

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Adrenocortical Tumors

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SUMMARY

Hormonally active tumors of the adrenal cortex are either benign adenomas or adenocarcinomas. They may be located within the adrenal gland or as adrenal rests along the Wolffian tract. Hyperplastic cortical tissue without actual neoplastic formation is also capable of elaborating excessive cortical secretions.

At the present state of knowledge, any one or a combination of the following compounds may be elaborated in a given case: the electrolytic, glucogenic, androgenic, or estrogenic corticosteroids.

Whether or not Cushing's syndrome is primarily pituitary or adrenal in origin is still a matter of conjecture.

FOR all practical clinical purposes tumors of the adrenal cortex may be classified as benign adenomas or adenocarcinomas. Sarcomas are mentioned frequently in the older textbooks, but several pathologists have assured the author that, if they occur at all, they are extremely rare.[14, 17, 18] It is felt that earlier observers perhaps mistook hypernephromas, or so-called Grawitz's tumors of the kidney, for sarcomatous neoplasms and, because of the vacuolized cells in such tumors with a "striking resemblance" to those of the adrenal cortex, assumed that they arose from cortical tissue.[24] There is another type of cortical neoplasm which should be mentioned, namely, those originating in adrenal rests along the Wolffian tract. While rare, these extra-adrenal hypersecreting tumors produce much the same clinical picture as those in situ. Since a patient with such a finding has recently come under the author's observation, this aspect of the subject will be discussed briefly in this presentation.

As to size, cortical tumors may range from mere granules, in an otherwise normal-appearing stroma, to retroperitoneal tumors so large as to misplace the entire abdominal contents. Moore[22] stated that "the frequency of local hyperplasia and adenomas of the adrenal cortex is in indirect ratio to the exactness of the criteria and examination. Most adrenals contain some type of spherical mass—grossly demonstrated nodules are present in about 10 per cent of all adults." Goldzieher[8, 9] and Grollman[12, 13] independently have stated that adenomatous nodules ranging from the size of small nests of cells to tumors the size of a hen's egg are observed in approximately one-third of all autopsies regardless of age or sex. Commons and Callaway[5] in an attempt to correlate the incidence of hypertension and diabetes with adrenocortical pathologic changes, encountered 216 tumors larger than 3 mm. in diameter in 7,434 consecutive autopsies (2.86 per cent).

If all these data are correct, it may be inferred that approximately 30 per cent of all adrenocortical neoplasms are smaller than a pea. Most, if not all, of the larger tumors are adenocarcinomas. The size of the neoplasm is no index of its secretory ability. Growths no larger than a hazelnut have produced profound alterations in the body economy, while those weighing a pound or more, although secretory, may exert barely discernible bodily changes. In fact, very large neoplasms have been found to be secreting tumors only after extirpation and examination. Most of the cortical adenomas are globular or egg-shaped and well set off from the remaining adrenal tissue though without the help of a connective tissue capsule. They are sulfur yellow in color and often contain darker yellow or brownish pigmented areas. Microscopically the cells may be arranged as in the normal cortex with the glomerulosa in the periphery and the fasciculata toward the center or, for some unknown reason, this arrangement may be completely reversed. The cells are abundant in lipoids which microscopically appear as vacuolized areas under the influence of solvents. Adenocarcinomas are soft growths of yellowish color prone to necrosis and hemorrhage.[9, 22]

Both the benign adenomas and the adenocarcinomas may be further subdivided into secretory and non-secretory tumors. Since the non-secreting varieties produce no demonstrable endocrine changes, they will not be dealt with in this presentation, which concerns neoplasms, both benign and malignant, that pour into the circulation sufficiently abnormal quantities of hormone to alter the body economy in a number of well recognized ways. However, an encapsulated neoplasm, whether benign or malignant, is not essential to cortical hyperfunction. Simple hyperplasia can and frequently does produce excessive amounts of cortical secretion with readily recognizable clinical results. While the hyperplasia may be bilateral, it is not uncommon to find contralateral hypoplasia in both simple hypertrophy and neoplastic disease. The latter finding, unless previously recognized, is an extra hazard to operation. On rare occasions metastatic tumors of the adrenal glands have been known to destroy the glands bilaterally with resultant Addison's disease.[27] Adrenocortical insufficiency has also been reported in persons who primarily presented evidence of Cush-

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ing's syndrome and in patients with precocious puberty.[4, 8, 3]

Confusion still exists as to what constitutes the classical clinical picture as a result of overproduction of cortical secretion. This is understandable in view of the many and varied biochemical factors involved. Here it is perhaps not amiss to give a clinician's viewpoint of the over-all picture as it appears at present. For, to understand even the fundamentals of the highly individualized steroids elaborated by the adrenal cortex is to realize that there is no single clinical picture of cortical overactivity, but rather various combinations of signs and symptoms, some most bizarre and seemingly paradoxical, which by inference implicate not only selective types of oversecretion but certain cytological structures as well. It is not yet possible to predict the cellular structure of a given neoplasm from the clinical picture encountered. However, this may not be far distant, since there is some experimental evidence to show that the zona glomerulosa secretes desoxycorticosteroids, which regulate fluid and electrolytic balance, and the zona fasciculata secretes 11-oxycorticosteroids which are concerned with gluconeogenesis, resistance to stress and the physiological mechanism of antibody production.[11]

While 27 or more compounds have been isolated from the adrenal cortex in crystalline form, at present four or perhaps five form the basis for most, if not all, clinical studies.[29] All of these are known to have been elaborated in greater or lesser quantities and in various combinations by both benign and malignant tumors. They are:

The electrolytic corticoids — Desoxycorticosterone, affecting mainly the balance of sodium, potassium, chloride and indirectly water, the overproduction of which results in the retention of salt and water, the excessive excretion of potassium—edema, hypertension and congestive heart failure.

The glucogenic corticoids — 17-hydroxy-11-dehydrocorticosterone (Compound E or cortisone), 11-dehydrocorticosterone (Compound A), corticosterone (Compound B), and 17-hydroxycorticosterone (Compound F), the overproduction of which results in muscular weakness, osteoporosis, a failing glucose tolerance, edema, fat deposits in the face and abdomen, amenorrhea, purplish striae of the skin, lymphopenia and eosinopenia, and a negative nitrogen balance.

The androgenic corticoids—Androstenedione, 11-hydroxy-isoandrosterone, androsterone and 17-hydroxyprogesterone, the overproduction of which produces masculinization of the female, lowering of the voice, amenorrhea, hypertrophy of the clitoris, acne, hirsutism, and occasional baldness; sexual and somatic precocity in the male child and heterologous changes in the female child.

The estrogenic corticoids—Estrone and progesterone, the overproduction of which produces feminization of the male, impotence, gynecomastia; homologous sexual precocity in the female child.

It is quite likely that as the various chemical compounds and their effects upon the body economy are elucidated, this list will grow. It is also to be hoped that some day the effects may be organized into regular clinical syndromes easy of recognition both as to pattern and etiologic delineation. At present, however, attempts at specific clinical classification leave much to be desired. Even the nomenclature is confused. A case in point is the classification of Kenyon,[19] which is as good as any and much better than most. He recognizes (1) the adrenogenital syndrome, (2) Cushing's syndrome, (3) mixed types including features of the two previously mentioned types, (4) a type characterized by a single endocrine manifestation, and (5) a type producing feminization of the male or homologous sexual precocity of the female.

The so-called adrenogenital syndrome must be considered first in the light of severity or degree. Where does normal function end and abnormal function begin so far as cortical function is concerned? Constitutionality alone plays a large part in the production of body type, body and facial hair, and even aberrant carbohydrate utilization. Many women of Russian-Jewish ancestry, as well as those of Mediterranean origin resemble, in a modified but sometimes rather startling manner, women who have Cushing's disease. Is their tendency toward trunk obesity, thin extremities, cervical kyphosis, hairiness and frequent family history of diabetes the result of inherent functional adrenocortical hyperactivity, or is this picture merely the reflection of the genetic type? Not so long ago, as a consultant, the author observed a moderately overweight young woman with facial, thigh and some chest hirsutism, who was being demonstrated as a patient with adrenocortical disease necessitating surgical treatment. However, when the patient was asked about her sister and mother, she said, "Both of them have more body hair than I." Obviously they did not all have adrenocortical disease. Frequently, however, it appears that hirsutism is not present in the mothers of such hairy females and that the tendency is apparently handed down from the male side of the family. It should be borne in mind that constitutional factors rather than adrenocortical, ovarian and testicular disease enter into some problems of homologous precocious puberty.

Aside from the factor of constitutionality and that of degree, the frank adrenogenital syndrome manifests itself differently according to the age of onset. Pseudohermaphroditism is said to be the result of adrenocortical hyperfunction in prenatal life. Pseudohermaphroditism has been produced experimentally in the offspring of pregnant animals which have been subjected to the administration of large doses of hormone.[10, 15, 28] One can see no reason why excessive production of either androgenic or estrogenic compounds would not produce sexual reverses in human fetal life; however, genetic deformities uninfluenced by sex hormones are so common elsewhere in the body as to argue against such etiological emphasis. If the so-called adrenogenital syndrome manifests itself early in life, it will produce sexual and somatic precocity of the masculine

type in young boys and heterologous changes or masculinization of the female. In adult women, amenorrhea, hypertrophy of the clitoris, atrophy of the breasts, body and facial hirsutism with alopecia of the scalp occur in varying degrees and combinations, while in the adult male only excessive masculinization is apparent.

It is next to impossible to discuss adrenocortical neoplasms without touching upon the perennial controversy concerning the primary cause of Cushing's syndrome.[7] There are two schools of thought: (1) that which clings to the theory that the primary disease is to be found in the adenohypophysis, as Cushing himself intended it to be, and that the adrenocortical lesions so commonly encountered are secondary to demonstrable cytological changes in this small but important organ; and (2) that which holds that the adrenal cortex is primarily involved and that the small basophilic adenomas and hyalinization or Crooke changes[6] in the cytoplasm frequently demonstrated in the adenohypophysis are merely the results of excessive cortical secretion. Both schools comprise experienced and conscientious observers.[1, 20, 3, 16, 21]

The fact that small basophilic adenomas of the anterior pituitary were found to be present rather frequently in persons in whom there was no clinical evidence of Cushing's disease,[23] while a number of patients with practically every symptom described by Cushing were discovered to have adrenocortical tumors, or cortical hyperplasia with few if any demonstrable changes in the pituitary, turned the tide in favor of the adrenal theory. The most recent (at least in print) champion of Cushing's original theory is Sosman,[25] by virtue of the fact that two out of six patients who had received roentgen irradiation to the pituitary, under his direction, have remained well for six years and 16 years. One patient, after pronounced improvement, had a relapse and died five years later, while one is living and apparently responding to treatment. Although the author for several years has been leaning toward belief in the primary involvement of the adrenal cortex, it must be admitted that the recently demonstrated potency and far-reaching clinical effects of the adrenocorticotropic hormone have somewhat shaken that belief. If under certain circumstances the adenohypophysis can pour into the circulation large amounts of this compound (ACTH) over a considerable period, almost anything could happen, especially to its target organ, the adrenal cortex. An overstimulated, hyperactive adrenal cortex could easily do the rest.

Cushing's syndrome, as it was originally known, consisted of a group of well recognized symptoms as follows: There was rapidly developing obesity of the face and trunk with concomitant atrophy of the extremities, purplish striae of the abdomen and flanks, purpuric and acneform eruptions of the skin, polycythemia, hypertension and decalcification especially of the spine, with early kyphosis. In addition, every female with this disorder that the author has observed has had, in a greater or lesser degree, some symptoms of masculinization such as excess facial and body hair, and occasionally amenorrhea, enlargement of the clitoris, and breast atrophy. It would therefore be difficult to recognize a clear-cut picture of Cushing's syndrome devoid of any or all of the evidences of the adrenogenital syndrome. It is also interesting to note that the administration of adrenocorticotropic hormone over long periods to arthritic patients produced the same untoward symptoms as prolonged cortisone administration, namely, the classical features of adrenocortical overactivity indistinguishable from the symptoms produced by hypersecreting adrenocortical neoplasms. It should also be noted that female patients so treated developed a degree of hirsutism and acne.[26]

Every patient with a frank adrenogenital syndrome, or the so-called corticometabolic syndrome (Cushing's disease) demands careful study. While the diagnosis can usually be made without difficulty at the time the patient seeks medical aid, the primary cause is frequently obscure. The physician must ask himself if the offending disease lies in the pituitary, the adrenal cortex, the thymus, in adrenal rests along the Wolffian tract, or perhaps in the fourth ventricle of the brain. Much depends upon the physician's attitude and therapeutic approach. A general physical and pelvic examination is, of course, essential. Studies of the urinary corticoids, ideal in all such problems, are still limited to endowed medical schools and institutions. Roentgenograms of the sella avail nothing since basophilic adenomas, if present, are too small, except in very rare instances, to present roentgen evidence of the disorder. Roentgenograms of the chest are essential in all patients to rule out enlargement of the thymus or neoplastic disease in the mediastinum. Roentgenograms of the skull, pelvis, spine and long bones may or may not reveal demineralization. Retrograde or even intravenous pyelograms may reveal a misplaced kidney, or on occasion be sufficient to outline a large adrenal tumor. Perirenal air insufflations in the adrenal area are used diagnostically by some physicians, but the procedure is considered relatively uninformative and even dangerous by others.

The 24-hour excretion of urinary 17-ketosteroids is more or less an index of the androgenicity of the cortical neoplasm. Values are usually considerably increased in the presence of malignancy with the predominant clinical picture of the adrenogenital syndrome. Moderately high values are found in benign adenomas, adrenal rests and simple hyperplasia, while values may be normal or only slightly elevated in Cushing's disease where virilism is a minor factor. A new and simple color test for dehydroisoandrosterone, said to be of value in the diagnosis of adenocortical tumors, has recently been devised.[2] The author has not had opportunity to evaluate it.

Other laboratory values vary according to the type and concentration of the elaborated secretions. The serum cholesterol, while frequently elevated, may be normal. There is usually a poor glucose tolerance with frequently a frank diabetic curve and

glycosuria. The basal metabolic rate and protein-bound iodine are frequently elevated. There may, or may not, be retention of sodium and chloride with potassium excretion resulting in hypertension.

If the corticogenital or corticometabolic syndrome is present and the offending lesion is not apparent, primary exploration by the abdominal route should be carried out. This gives opportunity to palpate both adrenals and to aid in the retroperitoneal extirpation of the adrenocortical neoplasm or hyperplasia, if and when discovered. In the female it also affords opportunity to see and palpate the ovaries and adjacent structures for adrenocortical rests and other virilizing neoplasms.

In addition to routine measures, patients undergoing cortical extirpation should be prepared by the administration of liberal quantities of the cortical hormone the day before, during and immediately following the operation. Large quantities of hormone are occasionally necessary for several days postoperatively to keep the patient from rapid collapse and death. Successful extirpation of the neoplasm results in amelioration or complete elimination of the entire symptom complex over a period of time.

CASE REPORTS

A girl 13½ years of age was referred because of a recent growth of hair on the face and sides of the neck. Although the patient came from a "very hairy family," her mother felt that this type and distribution of hair was probably not normal. The patient began to mature at 11 years of age—the breasts filled out to a moderate degree, and pubic and axillary hair appeared. She had never menstruated. When she was about 12½ years of age her voice began to change and to break on occasion like that of any adolescent boy. The psyche was preadolescent but entirely feminine. The patient was otherwise well.

Well developed and with normal feminine configuration, the patient was 65.5 inches in height, and weighed 127.7 pounds. There was abundant head hair, slight hairiness of the face and neck, and a male pubic escutcheon. The abdomen and legs had been shaved. Upon pelvic examination the vaginal introitus was noted to be small, but a sound could be inserted for approximately 3 inches. The clitoris was large and hooded, the labia were small. A small nodule which was believed to be an undeveloped uterus was noted in a rectal examination.

The basal metabolic rates were –21, –26. The blood cell count was normal except for moderate eosinophilia. There were no abnormalities in the urine and the blood values for cholesterol, protein-bound iodine, glucose tolerance, and icteric index were all within normal limits. Intravenous urograms and x-ray films of the skull were negative. The 17-ketosteroid excretion was 26.6 mg. in 24 hours (normal values for females, 8 to 13 mg.).

At first the patient was considered as having a benign adrenogenital syndrome and 5 mg. daily of stilbestrol was administered. In spite of gradually increasing the dosage up to 20 mg. daily, hirsutism became rapidly more pronounced. No withdrawal bleeding was produced. While large doses of stilbestrol were being given, the 24-hour 17-ketosteroid excretion at first dropped to around 10 mg., but approximately eight months after the initial examination, the values had risen to 42.6 mg. The face hirsutism had become increasingly embarrassing and exploratory operation was decided upon.

At laparotomy, performed about ten months after the patient first came under observation, the uterus was noted to be very small and undeveloped. The ovaries were small and sclerotic and the left ovary contained a cyst at the upper pole approximately 2 cm. in diameter. The cystic mass was excised and wedge-shaped biopsies were taken from both ovaries. The mass contained a mushy, yellowish material, similar to but not exactly like the material found in corpus luteum cysts. On palpation both adrenal glands appeared to be moderately hypertrophic. The postoperative course was uneventful.

The pathological report was as follows:

A mass 8 mm. in diameter removed from the left gonad revealed two blue-brown areas of tissue with attached capsule, each of which measured up to 2 cm. in greatest dimension. On section these masses were observed to consist of a group of clear cells resembling luteal cells but more like adrenocortical tissue containing a dusting of dark brown pigment.

Special stains were made to detect the presence of a hormone according to the method of Camber.* Fresh adrenal cortex was used as control. Positive pink-red stain for the presence of adrenocortical hormone was found in abundance in the ovarian tumor cells.

The wedges taken from the sclerotic but otherwise normal-appearing gonad sites contained numerous ova within a single layer zone of granulosa cells. None of them were stimulated to the formation of follicles or germinal hillocks. The findings were identical with those in normal prepubertal ovarian cortex.

The final diagnosis was adrenal cortex rest of left ovary.

Follow-up: The patient began menstruating two months after operation. The breasts gradually became larger, the uterus began to enlarge, the hair on the face, chest and arms gradually became finer and thinner, and the skin became soft and smooth. At the last observation, seven months after operation, the patient stated that she had been menstruating regularly. The cycle took 28 to 34 days with a four- to five-day period of rather scanty menses. The vaginal epithelial cells were well cornified and occurred in small sheets. The general configuration, psyche, and hair distribution were becoming more and more mature and feminine although the voice remained low.

* * *

A white married woman 36 years of age complained of a rapid gain in weight, from 128 pounds to 199 pounds since the birth of her last child, three years previously. Other complaints were of weakness, especially of the lower extremities, irregular menstruation, and hemorrhagic spots over the body.

Very obese, the patient was 63 inches in height, and weighed 189 pounds. Most of the weight was limited to the trunk; the arms and legs were relatively thin. There was also the characteristic kyphosis of the cervical spine so commonly seen in Cushing's syndrome. There was slight hirsutism of the face, but the distribution of hair over the body was otherwise normal. The blood pressure was 170 mm. of mercury systolic and 90 mm. diastolic. The heart appeared to be moderately enlarged in all diameters but the sounds were forceful and of good quality with a regular rhythm. Dark-bluish striae covered the abdomen. The liver appeared to be enlarged, the lower edge extending from 5 to 6 cm. below the costal margin on the right. It was not tender, and no nodules could be felt. Neither kidney could be palpated. Roentgenograms of the skull revealed a small, bridged sella turcica. Basal metabolic rates were zero. The urine, blood cell count, hemoglobin content, sedimentation rate and glucose tolerance were essentially normal. Cholesterol values

* Camber, B.: Histochemical demonstration of ketosteroids in the adrenal cortex, Nature, 163:285-286, Feb. 19, 1949.

were 277 mg. per 100 cc. of blood. Twenty-four hour excretion of urinary 17-ketosteroid was 5 mg. on one occasion and when repeated before operation was 2.6 mg. Air insufflation of the perirenal area was considered, but because of abdominal obesity and the advantage of more complete abdominal exploration, laparotomy was performed about eight months after the initial examination. The uterus was normal in size, firm in consistency and of regular contour. The right ovary was adherent to the posterior surface of the broad ligament. The liver was moderately enlarged, the gallbladder and spleen normal, the kidneys small. On the right adrenal gland was a walnut-sized mass which seemed to be circumscribed and much firmer than the surrounding tissue. The left adrenal gland was normal in size and consistency. The abdominal incision was closed without drainage and the tumor removed through a right subcostal incision.

Following the operation the patient went into shock and, in addition to routine measures, a large amount of adrenal cortex substitution was necessary. In all, 420 cc. of aqueous cortical extract and 16 cc. of lipo-adrenal cortex extract were administered in five days during the postoperative crisis.*

The pathological report was as follows:

The right adrenal gland contained a bright orange cortical tumor measuring 3.5 x 2.5 x 1.8 cm. At the edge of the adenoma there was evidence of dissection, and other fragments of this cortical tumor were submitted separately. There appeared to be compression of the subjacent adrenal gland, and section through the adrenal gland tissue revealed a central portion that was gray in color. Upon examination of sections, the tumor was noted to be rather uniformly bright yellow-orange in color, with focal areas of gray-tan in the central portion. The second portion of the specimen consisted of gray-tan lymph nodal structure obtained from the para-aortic area. The third portion consisted of fatty tissue also obtained from the para-aortic area.

Microscopic examination of sections through the compressed normal adrenal gland tissue including division of the cortex and medulla revealed these structures to appear essentially unchanged except for the fact that some of the adrenocortical cells appeared to contain a little less than the normal amount of fat. Lymphoid and fatty tissue without evidence of malignancy was noted in examination of sections through the second and third portions of the specimen.

Diagnosis: Benign adrenocortical adenoma, right adrenal gland.

Follow-up: The patient began losing weight shortly after leaving the hospital and in all lost approximately 30 pounds. Menstruation began two months after the operation. Many of the abdominal striae faded and most of the facial hair disappeared. The blood pressure was 130 mm. of mercury systolic and 90 mm. diastolic. The patient tired easily and was extremely sensitive to cold.

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Amebic Abscess of the Liver

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SUMMARY

In a review of the records in 50 cases of amebic abscess of the liver observed in the Canal Zone between 1920 and 1945 the following features were noted:

Incidence was preponderantly in males and highest in persons between the ages of 20 and 40. None of the patients was under 21 years of age.

There was a great variety of complaints at the time of admission to hospital. The most common was pain in the right upper quadrant of the abdomen.

Demonstration of either elevated or fixed diaphragm by x-ray film and fluoroscopic examination was useful in diagnosis in a number of cases, but absence of such findings did not rule out abscess of the liver.

In some cases there was history of previous dysentery with blood in the stools.

One or another of three operative procedures was used for drainage of abscesses in 39 patients. Of the 39, six died; in five of the six, multiple abscesses were present.

Emetine hydrochloride was given to all patients.

THE following is a study and analysis of 50 cases of amebic abscess of the liver in patients that were admitted to Gorgas Hospital, Ancon, Canal Zone, between the years 1920 and 1945. There are added in this article two illustrative case histories of patients treated by the author in 1947 and 1948 in northern Peru, South America.

After 1919 there was a sharp drop in the incidence of this disease in the Canal Zone, which is attributable to improvement of general sanitation measures and also to the use of the better methods of treating the cases of amebic dysentery, which reduced the hazard of amebic abscess. In the days of construction of the Panama Canal, the Japanese truck gardeners used human excreta for fertilizer. This was eventually forbidden, which probably accounts for a part of the decrease in incidence after 1919. The use of emetine hydrochloride was instituted at Gorgas Hospital at about this time. This also caused reduction in incidence of amebic abscess of the liver.

In the list of 50 cases occurring between 1920 and 1945, amebic abscess of the liver was diagnosed clinically in eight patients. Diagnostic aspiration was done in all eight cases but abscess was not demonstrated in any of them. The eight patients were treated with emetine and all of them responded satisfactorily.

This study is based primarily on the cases that appeared between 1920 and 1945, not inclusive of the eight in which the clinical diagnosis was amebic abscess of the liver.

The incidence was highest in persons between the ages of 20 and 40. There were no cases in persons under 21 years of age.

Although the disease was observed in patients of various nationality and racial background, in each case it occurred in an individual who had spent several years in a locality where there was a high incidence of amebiasis.

The distribution by sex was rather striking, in that in only one of the 42 cases was the patient a woman.

On admission to the hospital the patients had a great variety of complaints. The most constant chief complaint was pain in the right upper quadrant of the abdomen. A list of the complaints and the number of patients complaining of each follows:

Pain in right upper quadrant of abdomen	18
Generalized abdominal pain	9
Pressure pain in right chest	4
Fever	4
Bloody dysentery	3
Pain in left shoulder and epigastrium	2
Pain in right side of back	1

Several patients had symptoms and clinical findings of a very obscure nature at the time of admission, and abscesses were not demonstrated in them, or did not develop, until four to six weeks later. For example, one patient had symptoms typical of acute appendicitis. Appendectomy was performed immediately and the appendix was found to be normal. Two weeks later symptoms of abscess of the liver developed. Exploratory aspiration was performed and the abscess was drained. This patient was discharged as cured after 95 days in the hospital. Another patient was admitted with a complaint of fever and chills. On admission he was found to have tertian malaria and was treated accordingly. A few days later symptoms of pathologic change in the right upper quadrant of the abdomen were noted. Upon fluoroscopic examination of the chest it was noted that there was no movement of the right diaphragm, but it was not elevated. Exploratory aspiration was performed, an amebic abscess was found and drained, and the patient recovered.

Other significant complaints and the number of cases in which they were noted were: Diarrhea, 6; nausea and vomiting, 9; fever, 17; malaise, 1; indigestion, 1; chills, 5; anorexia, 6; night sweats, 1; cough, 1; headache, 1.

Physical findings in the large majority of cases were such as to localize the pathologic changes in the region of the liver. The findings and the number of cases in which they were noted: Tenderness and

rigidity in right upper quadrant, 24; enlarged liver, 17; abdominal distention, 3; generalized abdominal tenderness and rigidity, 5; elevated diaphragm, right, 1. In four cases there were no abnormalities noted upon physical examination at the time of admission.

A very helpful physical sign was the reaction to single finger percussion over the liver area of the chest and abdomen when abscess was suspected. At the point of maximum tenderness a needle was introduced for aspiration to establish the diagnosis.

A very useful procedure, at times, as an aid in diagnosis of this disease was the use of the x-ray film and fluoroscopic examination of the chest. In 11 cases either elevated or fixed diaphragm was noted upon x-ray examination. Demonstration of either of these conditions is highly indicative of subdiaphragmatic disease. However, absence of these findings does not rule out liver abscess, because they occur only in the early stage of the disease and only if the abscess is situated in the upper portion of the right lobe of the liver. If the abscess is located either in the left lobe or in the lower portion of the right lobe, the usual clinical finding will be enlargement and tenderness of the liver; and if the condition is allowed to go untreated, the inflammation will manifest itself in the upper regions of the abdominal wall.

In 11 cases there was history of previous dysentery with blood in the stool; in 31 cases there was no such history. In that total of 42 cases, there were ten in which amebae were found in the stool, and 31 in which amebae were not found. Other laboratory findings were not significant. Leukocytes in the blood at the most acute stage of the disease numbered from 6,000 to 30,000. Results of examination of the urine were of no particular aid in the diagnosis. The icteric index was elevated in only about one-fourth of the cases; the highest was 26 units.

One or another of three surgical procedures was followed in the treatment of most of the patients: (1) laparohepatotomy—extraperitoneal drainage of the abscess of either right or left lobe (17 patients); (2) thoracohepatotomy—extrapleural drainage with rib resection at the appropriate site (15 patients); (3) transthoracic hepatotomy—two-stage thoracohepatotomy (transdiaphragmatic) when the abscess was high in the dome of the right diaphragm (seven patients). Three patients were not operated upon.

Operative procedure to drain the abscess was carried out in 39 of the 42 cases in which a diagnosis of amebic abscess of the liver was established by operation or by autopsy. Six of the 39 patients (15.2 per cent) died, and five of the six were found at autopsy to have multiple abscesses. In the sixth case autopsy was not done. There were, then, 34 patients with single abscess of the liver who were operated upon, and in this group there was one death (2.9 per cent). Two of the six patients who died had been operated upon a second time when evidence of the presence of another abscess developed. In one of these two cases there was no other abscess found at autopsy, but there was extensive destruction of the liver. In the other case, many small abscesses in both lobes of the liver were noted at autopsy. A course of emetine hydrochloride was given to all patients. The usual course consisted of 0.3 gm. given subcutaneously twice a day for ten days.

Thirty of the patients had a single abscess in the right lobe of the liver, six had multiple abscesses, and six had a single abscess in the left lobe.

Cases of multiple abscess were extremely difficult to manage. In most cases not all of the abscesses could be drained. In cases of multiple abscess, the lesions were of various sizes and distribution. One patient had numerous abscesses in both lobes. Another had multiple abscesses in both lobes, one of which had been drained surgically; at autopsy another abscess 18 cm. in diameter was found which had not been drained. The third patient had 15 abscesses distributed through both lobes. The fourth had two large abscesses in the right lobe; one was drained and one was not. The fifth patient had hundreds of small and minute abscesses scattered throughout both lobes of the liver, and the sixth had two large abscesses in the right lobe.

All of the patients who were known to have multiple abscesses died. There were no deaths in the group of patients who had single abscess of the left lobe of the liver. There were three deaths among those who were considered to have a single abscess of the right lobe. In two of the latter cases autopsy was not done and there may have been more than one abscess, while in the remaining case of the three there was only one abscess but the patient was not operated upon. In this case the lesion was diagnosed roentgenologically with barium enema as an inoperable carcinoma of the transverse colon with hepatic metastases.

In all seven of the cases in which autopsy was done the presence of amebae in the wall of the abscess was noted.

Three of the patients in this series had associated ulcerative amebic colitis. They died.

The average hospital stay of those that recovered was 40 days. The shortest stay was 21 days and the longest 95 days.

In only two (5 per cent) of the cases in this study were there any of the usual serious complications of this disease. In one case, which terminated in death, one of the several abscesses of the liver ruptured into the peritoneal cavity just before operation. In the other case there was amebic pleural empyema in the right chest. The abscess had extended through the right diaphragm and the patient recovered following surgical drainage.

Two patients with amebic abscess of the liver were observed in Peru.

CASE REPORTS

CASE 1: The patient, a 46-year-old Peruvian farmer, was admitted to the hospital with complaint of constant, dull aching in the right upper quadrant which had been present for one week. This pain, during the last two days, had become somewhat more severe and the patient had been unable to continue working. Mild anorexia was associated with the pain.

The temperature was 100.5°F. The patient complained of

some soreness in the right shoulder. On deep inspiration there was a mild aggravation of pain in right side of the chest. Two weeks before admission and for a period of several days there had been a moderate attack of dysentery with blood in the stools. This condition subsided after a few days without treatment.

The patient was well developed and well nourished. Tenderness was noted on deep palpation in the right upper quadrant. Fist percussion over the lower right thorax produced sharp stabbing pain.

No abnormalities were noted in examination of the blood and urine. X-ray and fluoroscopic examinations of the chest were negative for pathologic change. A gallbladder examination by x-ray showed normal filling and emptying. The icteric index was 12 units. Repeated (five) stool examinations were negative for amebae.

During the first two days of hospitalization the pain became more intense with a continued elevation of temperature. Exploratory operation, with the possibility of amebic abscess of the liver considered, was done five days after admission. A transverse incision was made in the right upper abdomen. There was a soft, fluctuant area about 3 inches in diameter on the lateral aspect of the right lobe of the liver. About 35 cc. of thin, cloudy, reddish-brown fluid was aspirated from this area. Emetine solution, 0.6 gm. in 10 cc. of water, was reinjected into the cavity. A soft rubber tissue drain was placed between the right lobe of the liver and the abdominal wall and the incision was closed. The postoperative condition of the patient was considered good.

Emetine, 0.3 gm. twice daily, was given for the subsequent ten days. The drains were removed on the seventh day after operation, and the wound sutures were removed on the eighth postoperative day. The temperature and pain gradually subsided. On the tenth day the patient was out of bed and afterward made rapid improvement.

CASE 2: The patient, a Peruvian woman, 27 years of age, stated that three weeks previously she had had an attack of dysentery with blood in the stools which lasted for several days. Fever, nausea and pain in right upper quadrant developed at that time. The patient stated that she had been able to eat very little during the preceding three weeks and had lost a great deal of weight. During that time there had been occasional mild attacks of diarrhea without blood in the stool. Soon after the appearance of the pain in the right upper quadrant, the patient noticed swelling in the area, which had gradually become larger and more prominent.

Upon physical examination the patient was observed to be emaciated and apparently very ill. The skin was dry and the sclerae and skin were mildly icteric. The right diaphragm was elevated one interspace above the usual level. There was a bulging, soft mass in the right upper quadrant of the abdomen. In the center of this mass was an area about 2 inches in diameter over which the skin was thin and glistening as if an abscess were about to burst through.

The hemoglobin value in the blood was 42 per cent; erythrocytes numbered 2,225,000 and leukocytes 8,600. The icteric index was 21 units. Slightly elevated content of urobilinogen in the urine was noted. An x-ray film showed high elevation of the right diaphragm.

Supportive therapy, including intravenous administration of fluid and whole blood, was started immediately. At operation the following day brown-colored pus was encountered immediately under the skin. Suction drainage was used to evacuate the cavity, which was estimated to be 20 cm. in diameter in the greatest dimension. It was evident at that time that there was a great deal of destruction of the liver.

The patient was given emetine subcutaneously, 0.3 gm. twice a day for ten days, and supportive therapy was continued. During the first week after operation there was moderate improvement in that the patient regained some desire to eat and said that she felt somewhat better. The temperature dropped and for a few days remained at 99.6 degrees. It rose gradually during the next two days and an x-ray film of the chest made at that time showed there had been further elevation of the diaphragm. The eighth rib was resected to reach and drain a second abscess. There was only slight improvement following this procedure and even though blood transfusions, emetine and antibiotics were used the patient gradually became weaker and died four weeks after admission.

DISCUSSION

The prognosis for patients with a single amebic abscess of the liver is excellent and the number cured should approach 100 per cent in any series. In the presence of multiple abscess the mortality rate increases. Craig[1] in 1934 considered the prognosis grave in this disease and expected an over-all mortality rate of 25 to 30 per cent when all cases, both single and multiple abscesses, were included.

The mortality rate also will be affected by the general physical condition of the patient when first observed, by how early proper treatment is begun, and by the extent of damage to the liver.

Ochsner and DeBakey[3] in 1935 reported an over-all mortality rate of only 4.1 per cent in their series. This greatly influenced the change from open surgical drainage to that of repeated aspiration of the abscess cavity and subcutaneous injection of emetine hydrochloride. However, not all cases can be handled by this comparatively simple procedure. Manson-Bahr in 1945 reported that open surgical drainage was necessary in about 25 per cent of cases observed by him.

The use of open surgical procedure should be considered when: (1) it is demonstrated that an abscess has become secondarily infected; (2) it is considered inadvisable to pass an exploratory needle through an uncontaminated body cavity or into a dangerous area; (3) an abscess "points" in the epigastrium, that is, is situated in the left lobe of the liver; (4) an abscess has not responded to the aspiration method; (5) no pus is obtained after repeated aspirations although indications of the presence of pus are strong.

Open surgical drainage with emetine injected subcutaneously was the method used by the author because it had apparently been producing satisfactory results.

It is recommended, however, that the treatment as outlined by Ochsner and DeBakey[3] of repeated aspiration of the abscess and subcutaneous injections of emetine be considered the method of choice in cases of amebic abscess of the liver and that the open surgical drainage procedures be used only as indicated in the preceding paragraph.

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Rehabilitation of Patients with Hemiplegia

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SUMMARY

Many patients with hemiplegia can be rehabilitated. Physiological reflexes may be used in attempting to establish patterns of motion and are of definite aid in overcoming contractures. Physical and occupational therapy is of value.

PATIENTS with hemiplegia can be rehabilitated unless one or another of the following conditions exists: Senility, medical complications prohibiting activity, loss of learning ability, psychosis, lack of motivation, and (sometimes) atonicity.

In senile patients the protoplasm cannot meet the requirements of active existence and the organic structures of the body are worn out. The weakness of senility must be differentiated from atrophy of disuse, which can occur at any age and is correctable by exercise. The physiological age must not be confused with the chronological age. It is not uncommon to observe one patient who is 70 years of age to be physiologically younger than another who is 65 years old. Therefore, if the individual is physiologically capable, the chronological age is of no importance in relation to rehabilitation.

Medical conditions prohibiting rehabilitation include active intracranial bleeding and acute heart failure. Chronic heart failure is not a contraindication, providing activity is maintained within the limitations of cardiac compensation.

Loss of learning ability is the commonest stumbling-block encountered in patients who do not respond to rehabilitation efforts. The status of this particular faculty may be determined by psychological testing. By a variety of tests, the ability to remember may be conclusively established.[6] If the testing results are equivocal, therapeutic trial is indicated. Aphasia must not be mistaken for loss of learning ability. The aphasic patient may have an interruption in sensory reception or motor expression without any interference with memory centers.

Motivation is the keystone of rehabilitation. It is of two main types, (1) internal, and (2) external.[7] In internal motivation the impetus to activity arises from within the individual; in external motivation the impetus is provided from the outside. Internal motivation is frequently lost in chronic debilitating illnesses. In order to renew it, external motivation must be supplied as a stimulus. This is accomplished by demonstrating to the patient that he is capable of performing a movement which he did not consider possible. The realization that motion is possible serves as a stimulus to internal motivation.

Atonicity or flaccidity may be a barrier to rehabilitation. In many cases, however, the patient may be made ambulatory with the aid of a long leg brace.

Rehabilitation is started as soon as medical condition warrants. In cases in which paralysis has been caused by cerebral hemorrhage, activity must wait until all evidence of bleeding ceases. Patients who have had cerebral embolism or thrombosis can be started on treatment within 48 to 96 hours. Initially, atonicity is usually present. This pseudoflaccid stage later changes to a spastic stage. The muscles on the involved side begin to atrophy immediately as the result of disuse. The involved muscles will respond, by contraction, to electrical stimulation. Electrical stimulation can delay atrophy even in muscles in which peripheral nerves have been severed.[3, 5] Therefore, to minimize atrophy of disuse, the paretic muscles are electrically stimulated. In the later stages when hypertonicity appears, and with it some degree of voluntary motion, electrical stimulation is no longer indicated. The patient is then capable of performing some degree of voluntary effort.

During the atonic phase, it is important to maintain the range of motion in the joints. Contractures are liable to develop, particularly in older individuals. The most common site of contracture is the shoulder. Contracture of the ankle in plantar flexion, while relatively common, is more apparent than real. This will be dealt with in greater detail later. At this stage, motility is maintained by passively moving each joint through a complete range of motion. This procedure is performed at least once a day.

Teaching the patient the activities of daily living[2] is started at the onset of treatment. These activities consist of functions which are inherent in everyday existence, such as getting out of bed, standing, dressing, eating, and walking.

With the return of tone in the involved muscles, there is also some return of voluntary motion. The amount of voluntary motion is variable and depends on the site and size of the cerebral lesion. It has been pointed out[9] that the loss of willed movements is in proportion to the failure of the activating influence of the receptors to reach the motor mechanism through the pyramidal tract. Thus the long-lasting movements which are dependent upon sensory guidance suffer most. The arm suffers more than the leg, and the hand more than the arm. Furthermore, there seems to be a direct relation be-

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tween the degree of loss of voluntary movement and the degree of hypertonus. The greater the tonicity, the less the willed movement.

Hypertonicity in the legs affects the extensor muscles so that the knee is held extended and the foot is plantar-flexed and inverted. When the patient tries to walk there is an apparent foot drop, which prevents the leg's being carried through during the step. As a result the patient elevates the pelvis and tends to abduct the leg on the affected side while walking. A short leg brace with a 90° ankle stop is a definite aid in counteracting these effects. Patients with mild ankle clonus need only a light spring brace. If the clonus is more severe, a double bar brace is necessary.

There are several methods of training the step. One consists of applying pressure over the knee of the seated patient as he attempts to flex his hip. This stimulates the stretch reflex. Another method, for patients incapable of voluntary hip flexion, is the application of painful stimulus such as may be caused by bending down the toe.[4] The reaction is really a withdrawal reflex in response to a painful stimulus, as was shown by Sherrington on decerebrate animals. Kabat[8] expressed the belief that a pattern of motion may be established by constant repetition. When either the stretch or the withdrawal reflex is elicited, the hip, the knee and the ankle dorsiflex, and the foot everts. Apparent plantar flexion ankle contracture will disappear. In those cases in which true ankle contracture exists, reflex action may be used as an aid in stretching the contracture.

Parallel bars may be used in teaching ambulation. The patient first learns to stand and then to walk. Bars are better for this purpose than walkers, since they give the patient a sense of security in that he has something stable to grasp. From the bars the patient is graduated to a cane and finally may be able to walk without support.

Paresis of the arm is more difficult to overcome. Nevertheless good functional recovery as a result of overcoming atrophy of disuse is not uncommon. The tonic neck reflex (turning the head toward the involved side) may be used to aid in activation of the arm. It has been demonstrated that the strength of forward flexion and elbow extension can be increased by over 300 per cent when the tonic neck reflex is used to reinforce voluntary motion. In addition, strength in the arm can be further increased by as much as 200 per cent by overcoming atrophy of disuse in the course of treatment.[10]

The so-called "frozen shoulder," which not only interferes with the range of motion of the arm but is also a source of pain, may be treated by Mennel manipulations and by passive stretching. If the tonic neck reflex is utilized during the treatment of the frozen shoulder, an increase of 10° to 20° of forward flexion, abduction and external rotation may be obtained on passive movement. If the tonic neck reflex is neglected during stretching, the spasticity tending to produce adduction and internal rotation remains to be overcome. The range of motion attained may be maintained by pulley exercises. Here again the tonic neck reflex is of definite aid.

Occupational therapy procedures, which have the advantage of keeping the patient interested in improvement, are best suited to treatment of the arm. Functional treatment by occupational exercise should be started with the arm at shoulder level.[1, 11] The arm may be supported either on a table or by a sling suspension. Resistance is added as tolerated. With increase in strength, the support may be lowered so that work is done at a lower level, and ultimately the support may be removed. Then working position of the unsupported arm may be gradually raised so that it has to be held against gravity.

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Toxicology of Organic Phosphate Insecticides

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SUMMARY

The development of effective new insecticides has created potential industrial health hazards to people engaged in their manufacture and application, as well as to those with casual exposures. A group of these insecticides known as the organic phosphates is extremely toxic, destroying the enzyme cholinesterase and exerting a cholinergic action on the mammalian animal. A discussion of the origin, chemistry, and pharmacology of these compounds, along with a description of symptoms, diagnosis and treatment of poisoning is presented. Methods of prevention of poisoning and control measures for the safe use of these compounds are described.

INTENSIVE research in the development of new insecticides in the last few years has resulted in products such as DDT, DDD, chlordane and others which have proven to be a boon to agriculture and in the campaign against insect-borne diseases. However, these new compounds, besides being effective insect killers, are also toxic to humans and can be dangerous if improperly handled. Most recently a new group of compounds, the organic phosphates, has come into use and represents a potential threat to human beings.

Hexaethyl tetraphosphate (HETP) was developed in Germany, where it was known as "Bladan" and was considered for possible use in chemical warfare. Tetraethyl pyrophosphate (TEPP), also known under the name of Vapotone and other commercial designations, is the active toxic ingredient in HETP and was independently developed at the University of Chicago a short time ago.[8] Both these compounds are heavy, syrupy liquids freely miscible with water. On contact with moisture they readily hydrolyze and lose their toxicity; hence, unlike DDT, they have little residual action.

A third organic phosphate is parathion (also known as Thiophos, Alkron and by other commercial names) which is a deep brown liquid of low vapor pressure, some samples of which possess a characteristic odor. Chemically it is O, diethyl O, P-nitrophenyl thiophosphate. It is slightly soluble in water but completely miscible in many organic solvents including ethers, alcohols, and animal and vegetable oils. It is stable in a neutral solution but is rapidly hydrolized in the presence of alkalies, including soap. In actual application as an insecticide, the material may be used as a wettable powder or a dust.

The organic phosphates are very effective in the control of a number of different pests. They are being widely used in the control of mites, codling moths, and other insects which may be resistant to DDT and the older insecticides.[7] Application to fruit orchards and other crops is made by a variety of means, including airplane spraying, mechanical spraying from tractors, and hand spraying.

In the period between January 1, 1948, and August 31, 1949, there were 49 cases of organic phosphate poisoning reported to the California State Department of Public Health, Bureau of Adult Health. One case was fatal. Three deaths due to parathion poisoning in other parts of the country were reported by Hamblin in May 1949,[4] and since that time the authors have had reports of two other fatalities outside of California. Faust[3] reported a typical case of tetraethyl pyrophosphate poisoning in September 1949. Poisoning has occurred among people engaged in the manufacture of these materials, in those compounding solutions containing them, in airplane pilots dusting crops, in agricultural workers, and in people inadvertently exposed (one such was a welder who cut into a pipe containing parathion).

PHARMACOLOGY

In experimental animals it has been demonstrated that the organic phosphates are readily absorbed through the intact skin and from the respiratory and digestive tracts.[5] In all reported cases in humans, absorption was through the skin or respiratory tract, and symptoms appeared within a brief period after exposure, indicating rapid uptake by the body. The compounds themselves are only slightly irritating when first applied to the skin, so there is no immediate warning sign as to the potential danger. If splashed in the eye, there is an intense miosis, resulting in temporary blindness.

The principal mode of action of the organic phosphates is the inactivation or destruction of the enzyme cholinesterase, producing a cholinergic action in mammals.[2] The muscarine-like effect is the underlying cause of the multitude of symptoms which have been recorded by various investigators throughout the country.

SIGNS AND SYMPTOMS

Observed cases have varied from those in which symptoms were mild and transient to those in which severe toxemia resulted in death. Early signs and symptoms include headache, nausea, vomiting, diz-

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ziness, cramps, and constriction of the pupils. More severe poisoning is manifested by a feeling of tightness of the chest, diarrhea, difficulty in breathing, fibrillary twitching of the voluntary muscles, convulsions, and coma.

Death in acute poisoning may be due to any one of the following mechanisms:

1. Bronchial constriction with an outpouring of mucous secretions resulting in mechanical asphyxiation.
2. Central nervous system stimulation and eventual irreversible depression.
3. Stimulation and eventual depression of neuromuscular junctions.
4. Accidents occurring as a result of the visual or mental impairment.

Evidence concerning chronic toxicity and cumulative action is incomplete. However, studies are now under way to determine the effect of chronic exposure to dosages below those producing acute effects. It may be that with chronic exposure an irreversible destruction of cholinesterase can be produced. Experimental animals receiving sublethal doses have survived with no residual damage, presumably because they were able to reproduce enough cholinesterase to replace the amount destroyed by the insecticide.[6] However, further studies on this point are necessary.[1]

At present, diagnosis of intoxication with one of these compounds depends mainly on an awareness of the syndrome and on a high index of suspicion in areas where the chemicals are being used. Any person who may have come into contact with an insecticide, complaining of "blindness," blurred vision, headache, tightness of the chest or any other symptom listed above, should be suspected of acute organic phosphate intoxication. A laboratory finding of reduced cholinesterase activity in the plasma or erythrocytes is confirmatory evidence. However, interpretation of blood cholinesterase levels is difficult.

TREATMENT

Atropine is a specific therapeutic agent against the parasympathetic stimulation. Large doses (1 to 2 mg.) should be administered early and repeated frequently as indicated by the clinical picture. Postural drainage, and suction if available, should be used to remove the excess bronchial secretions and maintain a patent airway. Artificial respiration should be employed if breathing has ceased, and the concomitant use of oxygen may be life-saving.

The following reports are presented to illustrate the signs and symptoms of the disease, as well as the diversity of occupational exposures that have resulted in organic phosphate poisoning:

CASE REPORTS

A 31-year-old white male entomologist, employed by an agricultural experimental station, had been working with parathion intermittently for four months. One morning he arrived at an orchard shortly after 9 o'clock and took charge of the application of parathion which was already in progress. Fruit trees were being sprayed with a mixture containing 2 pounds of parathion (a 25 per cent wettable powder) per 100 gallons of water at the rate of 25 gallons per tree. The patient ran the sprayer while an assistant operated the tank and weighed and measured the ingredients. The sprayer had to be refilled about every 15 minutes, and at the refilling the patient added the ten pounds of powder containing parathion to the tank as the water was being pumped in. During the operation of the sprayer he was constantly exposed to drizzle of the spray. During the morning, he wore no protective clothing or mask other than wrist-length gloves. At noontime he reported to other personnel on the job that everything had proceeded satisfactorily but that he had a headache. In answer to specific inquiries he assured his co-workers that his headache was not severe and probably of no consequence. He went home to lunch and upon returning he was wearing a pair of coveralls in addition to cap, boots and gloves. At 3:25 the manager of the orchard visited the operations and had a conversation with the patient, who in no way indicated that he was aware of any reaction to the material.

The spray operation continued until approximately 4:05 p.m., at which time the patient informed his assistant that he felt dizzy. A few minutes later, while the assistant was cleaning the equipment, the patient became nauseated and vomited. He at first rejected a suggestion that he leave the orchard, but shortly thereafter he got into his car and started to drive home. He drove about a quarter of a mile and again became nauseated. He asked a young man to drive him home and arrived at his house at about 4:45 p.m. and told his wife that he was ill from parathion. He asked her to call a physician and ambulance and to instruct the ambulance to bring an oxygen tent. In the meantime, after help in undressing, he bathed. The physician arrived shortly after 5:00 p.m. and pronounced the patient dead at approximately 5:05 p.m. At no time during his brief illness did the patient receive atropine.

Autopsy did not reveal any other contributing information as to the cause of death, and it was attributed to poisoning by parathion. A postmortem specimen of blood showed no cholinesterase activity and contained one part of parathion per million parts of blood.

* * *

On July 8, 1949, at 8 a.m., three picking crews of 30 men each went into orchards to pick fruit. Two crews were assigned to blocks in the orchard which had been sprayed on June 27, 1949, with parathion spray powder, enough to give 2½ pounds of parathion per acre. The other crew went to a block sprayed on an earlier date.

The day became hot and sultry, with no breeze; the temperature was between 90° and 100°F. Between 12:30 p.m. and 8 p.m. 22 of the pickers working in the most recently sprayed blocks felt ill and quit work to lie down. Most of the men began to vomit. All 22 were taken to the nearest hospital where it was noted that they all had headache, pallor, nausea, vomiting and weakness, and that two or three complained of twitching of arm and leg muscles. They were all given 0.6 mg. of atropine sulfate intramuscularly. In 20 to 30 minutes all improved and vomiting ceased. Ten of the men were permitted to go home that evening, and the remainder who stayed overnight for observation were released the next morning.

Results of urinalysis in all cases were normal. In all cases there was a slight decrease in erythrocyte count and hemoglobin content, while leukocytes numbered between 14,000 and 20,000. Because of lack of facilities, blood cholinesterase determinations were not made.

Most of the men had taken their own lunches from home. Three or four had eaten at the mess hall provided in the orchard. Some had eaten pears from the orchard and others

had not; some had drunk from new containers and some from old containers of water. There was no evidence of any common food or any common source of water supply which was consumed by all of the men. The diagnosis in all cases was acute parathion poisoning caused by inhalation of vapors resulting from spray residue remaining from the spraying which had been done 11 days previously.

Reports of the remaining cases are presented in tabular form.

PREVENTION

Poisoning by this compound can be prevented if proper attention is given to safe methods of handling it and if all persons concerned appreciate its extreme toxicity. All contact with the bare skin must be avoided and natural rubber gloves must be worn when handling parathion. If any of the material gets on the skin it should be thoroughly and

Summary of Data Regarding Cases of Parathion Poisoning Reported to the California State Department of Public Health January 1, 1948, to August 31, 1949

Date	Type of Exposure	Signs and Symptoms	Remarks
1948	Spraying oranges with HETP.	Miosis, with partial loss of vision for 72 hours.	
1948	Spraying oranges with HETP.	Miosis, with partial loss of vision for 8 hours.	
1948	Pilot spraying from airplane with HETP. Refilled hopper several times.	Crashed. Had complained of poor vision during reloading.	Cause of crash not certain but believed to be due to miosis.
1948	Spraying nursery with HETP.	Pupillary constriction for 12 hours, tightness of throat.	
1948	Spraying citrus orchard with HETP and TEPP.	Pupillary constriction. Pulmonary congestion. Pharyngitis.	
1948	Spraying nursery and fruit trees with HETP and TEPP.	Pupillary constriction. Dyspnea.	
1948	Spraying field crop with TEPP.	Miosis; tunnel vision; lacrimation; tightness of chest. Diarrhea.	
1948	Spraying berries from helicopter with TEPP.	Miosis lasting 72 hours. Constriction of chest.	
1948	10-year-old, by observing pest control operator apply TEPP under and around house.	Headache; miosis; nausea; vomiting; muscular twitching. Hospitalized 40 days.	
1948	Smoking orchard with TEPP.	Tracheitis.	
8-25-49	Spraying beans with TEPP.	Substernal burning and tightness.	
8-12-48	Spraying beans with TEPP.	Dizziness, nausea, vomiting, tightness of chest.	
7- 1-49	Spraying from helicopter with TEPP.	Helicopter crashed. Pilot had pinpoint pupils lasting 4 days.	
10-15-48	Spraying with parathion.	Headache, weakness, nausea, perspiration.	
6-27-49	Mixed 15 per cent parathion powder with water and delivered to sprayers. Operated nurse rig.	Dizziness, nausea, vomiting, abdominal cramps, perspiration. Dyspnea; apprehension. Miosis. Auricular fibrillation.	Recovered with treatment with atropine, oxygen, calcium gluconate.
6-30-49	Mixed 15 per cent parathion powder with water and delivered to sprayers. Operated nurse rig.	Nausea, vomiting, miosis, dyspnea. Cyanosis, loss of consciousness. Fibrillary twitching of voluntary muscles.	Recovered with treatment with atropine, oxygen, calcium gluconate.
12- 3-48	Spraying with 1 lb. 15 per cent parathion—100 gallons of water. Spray got on face and chest.	Nausea. Tightness of chest. Heaviness of arms.	Myocardial infarction suspected but EKG normal.
Sept. 1948	Spraying with parathion from 6 a.m. to 2 p.m. on very hot day.	Started at 4 p.m. on day of spraying. Headache; miosis; nausea; vomiting; muscle spasm of legs; convulsions; coma.	Hospitalized five days. Recovered with atropine treatment. Loss of 20 lbs. weight.
8- 6-49	Pruning trees which had been sprayed with parathion 7 days earlier.	Weakness; nausea; vomiting. Hypotension (80/50); bradycardia. Athetoid movements. Pain in right hand.	Good response to atropine.
4- 6-49	Female employee packaging 25 per cent wettable powder parathion in a chemical plant.	Became ill at home several hours after exposure. Chest pain; diarrhea; weakness.	Good response to atropine. Low plasma cholinesterase activity during illness.

(Table continued on next page.)

(Continued from preceding page.)

Date	Type of Exposure	Signs and Symptoms	Remarks
June, 1949	Spraying with parathion.	Headache; nausea; vomiting; abdominal cramps; dyspnea; cough; frothy sputum.	
May, 1949	Welding and cut into a pipe containing parathion.	Onset within ten minutes; nausea; vomiting; vertigo; headache.	Hospitalized one day.
Aug., 1949	Had sprayed with parathion, HETP, TEPP, and other insecticides intermittently for 2½ years. Mixed sprays and weighed out wettable powder.	Headache; diarrhea; nausea; vomiting; anorexia.	Insidious onset. Low plasma cholinesterase.
7-27-49	Night superintendent in plant that packages parathion.	Nausea; vomiting; headache; following packaging of parathion.	
8-12-49	Crop dusting with parathion.	Dry skin; nausea; chest pain; pallor and apprehension.	
6-30-49	Spraying crops with parathion.	Nausea; salivation; perspiration.	
9-15-49	Foreman in nursery where parathion was sprayed.	Nausea; myalgia; miosis; dyspnea, diarrhea.	Good response to atropine.
7- 8-49	22 pickers working in an orchard that had been sprayed on June 27, 1949. Very hot day. Onset of symptoms 4½ to 12 hours after picking started.	Pallor; nausea; vomiting; sweating; weakness. W.B.C. elevated. R.B.C. lowered. Urinalyses negative.	Remarkably rapid response to atropine.
8-23-49	Sprayed fruit grove with parathion all day. Drove tractor and made up parathion solution.	Headache; vertigo; nausea; vomiting. Death occurred 8 hours after starting work.	Received no treatment. Dead on arrival of M.D. Postmortem blood had no cholinesterase activity.

quickly washed off with copious amounts of soap and water. Workmen should be provided with freshly laundered coveralls and should wear fresh clothing each day, including socks and underwear. In addition, sprayers or others who are likely to be drenched with the chemical should be provided with a cellophane cape and hat or other liquid-repellent garment, as ordinary clothing will prove to be merely a reservoir for further absorption. Inhalation should be avoided by use of a chemical cartridge respirator, full face-piece type equipped with GMC-1 canister.* Workers should bathe with soap and water after using the material, and contamination of food and tobacco should be avoided. An added safeguard is to avoid prolonged exposure. This may be accomplished by rotating workers on different job assignments so that no one worker deals with the organic phosphates day after day for a long period.

The question has arisen as to the wisdom of providing atropine to exposed workers, to be taken if symptoms of poisoning occur. The proponents of this procedure argue that it may be life-saving, while others feel that it would lead to self-medication in many cases where symptoms were due to something other than organic phosphate poisoning. A practical procedure may be to leave a small supply of atropine with a foreman or other responsible person, who should be instructed to telephone a physician should symptoms develop in any exposed workers. He could then be informed whether or not to administer the atropine while waiting for the doctor's arrival.

To date, no cases of poisoning due to ingestion of food sprayed with these materials have occurred. It is recommended that there be at least a 30-day interval between application of parathion and harvesting of the crop. If this is heeded, it is believed that there is no danger to the consumer.

*Sprayers should check with their local health department or department of agriculture for the best kind of respirator.

Grateful acknowledgment is made to the many physicians who have supplied information about cases which they have diagnosed and treated.

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CASE REPORTS

Homologous Serum Hepatitis Following Operation on the Biliary Tract

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Report of Three Cases

WITH the ever-increasing use of transfusions of blood and plasma, and the use of blood products, it is pertinent to emphasize that homologous serum hepatitis may follow these procedures and may confuse the issue in diagnosis, especially in biliary tract disease. Since it may occur following operation on the biliary tract in cases in which jaundice was present before operation, if jaundice should recur two to six months postoperatively the surgeon should be alert to the possibility of serum hepatitis as a cause, lest unnecessary reoperation be done.

Brightman[2] and Neefe[5] have described the clinical aspects of homologous serum hepatitis and have adequately reviewed the literature. It is now evident that the pooling of plasma and blood in commercial and hospital blood banks increases the risk of infecting patients with the virus of hepatitis. Because of the prolonged incubation period (two to six months) the relationship between the administration of blood or plasma and the subsequent development of jaundice in hepatitis may be overlooked. Brightman[2] noted that the New York State Department of Health in 1947 reported that hepatitis developed in 29 of 649 patients followed for six months after receiving American Red Cross surplus plasma, an incidence of 4.5 per cent. This was lower than the 7.3 per cent incidence noted by Spurling[8] in England. Scheinberg[6] reported the mortality rate from homologous serum hepatitis at Peter Bent Brigham Hospital in 1945 was 36 per cent.

The committee on blood and blood derivatives of the American Red Cross[1] urged that plasma be used only in those emergencies in which safer agents such as whole blood or serum albumin are not available, and recommended that patients who have received human plasma or serum should not serve as donors within six months afterward, even though they felt perfectly well. It is necessary to regard a recent transfusion or the recent use of human serum as significant etiologically when any patient with jaundice is being studied.

Schiff[7] emphasized the importance of homologous serum hepatitis in the differential diagnosis of jaundice, with particular respect to (a) metastatic neoplasm of the liver in patients who have had a recent resection of a malignant tumor and who received blood or plasma; (b) stricture or stone of the common duct in patients who have had recent operations upon the biliary tract, usually cholecystectomy, and (c) neoplasm as a cause of painless jaundice in middle-aged or older people. He reported six cases in detail. He observed 11 cases in one year.

When the surgeon is confronted with recurrent jaundice in a patient upon whom he has recently operated to extract stones from the common bile duct, it is important to accurately establish whether the jaundice is on the basis of obstruction again or is due to the virus of hepatitis.

Following are reports of three cases in which jaundice recurred following common duct operation and was due to homologous serum hepatitis.

CASE REPORTS

CASE 1: A 42-year-old physician was discharged from the army because of severe recurrent attacks of precordial pain associated with nausea and vomiting. The patient had never had an operation. He had had attacks of severe upper abdominal pain since 1941.

Results of extensive laboratory and cardiovascular studies were within normal limits. In August 1946, the patient first noted jaundice and was admitted to the Cedars of Lebanon Hospital. There was no fever. Pronounced tenderness in the right upper quadrant of the abdomen was noted. The icteric index was 32 units and it rose within a few days to 38 units. The blood protein level was depressed to 5.4 gm. per 100 cc. An electrocardiogram was normal.

At operation August 23, 1946, the gallbladder, which was thickened and contained stones, was removed. Four large stones were removed from the common bile duct. A T-tube was inserted into the common duct. The appendix was removed and the abdomen was closed. During and after the operation, the patient received 500 cc. of whole blood (individual donor) and 500 cc. of pooled plasma. The icteric index slowly declined. The patient was discharged from the hospital September 7, 1946, much improved. Cholangiograms a few days later showed the common bile duct to be patent and the T-tube was removed. There was no further drainage. The icteric index was normal by September 24 and the patient had made a normal recovery. Thirty-eight days after the operation, scleral icterus was noted again. It became progressively more severe and was associated with nausea and upper abdominal distress. The urine became dark, the stools lighter. Increased fatigability was noted by the patient. There was no pruritus. Because of the presence of bile in the stools, a diagnosis of hepatitis was entertained. The patient wished to go to Minnesota for further study. The following is a summary of the findings from the University of Minnesota Hospital:

The patient was moderately icteric and not acutely ill. There were no masses palpable in the abdomen. The liver was thought to be somewhat smaller than normal. The immediate impression was of recurrence of common duct stone.

The hemoglobin content on admission was 12.7 gm. per 100 cc. of blood. Leukocytes numbered 5,200 with 72 per cent neutrophils and 25 per cent lymphocytes. The blood urea nitrogen level was 12 mg. per 100 cc. The plasma

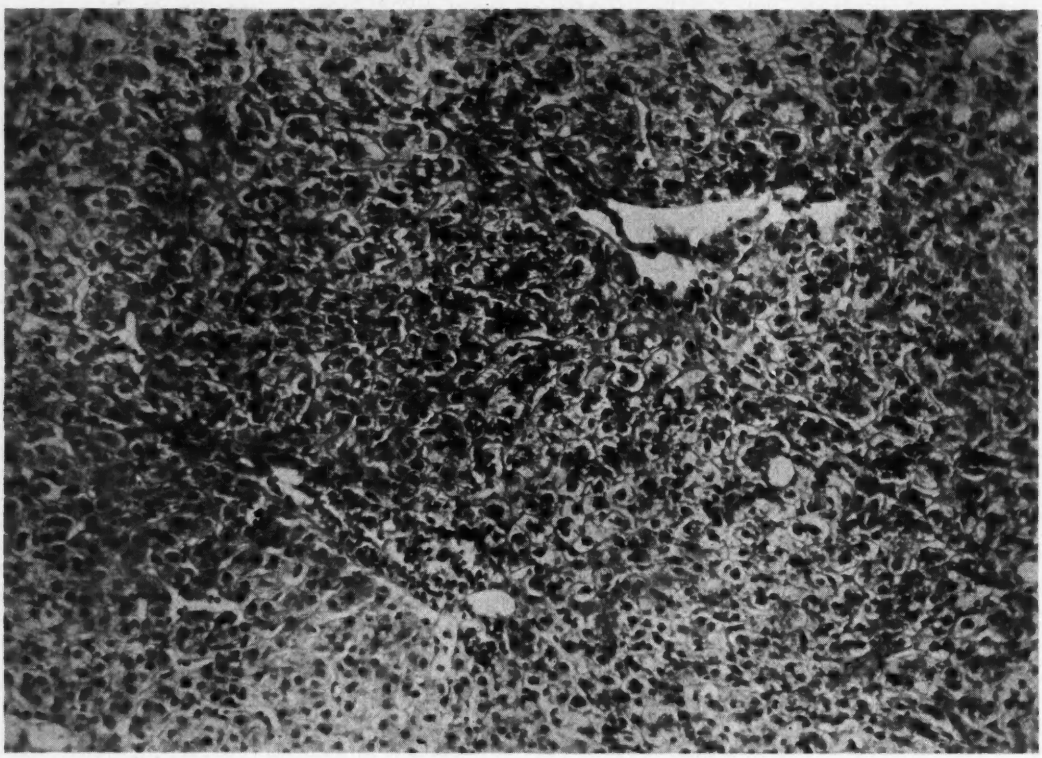

Figure 1.—Microphotograph, *Case 1:* Low-power field showing disorganized pattern of hepatic cells, diffuse bile thrombi—mostly intracellular—cytoplasmic vacuolation and slight reticulum-cell hyperplasia. Within lobules there is no significant inflammatory cell infiltration.

content of proteins was 6 gm. per 100 cc. However, liver function data was strongly suggestive of jaundice of parenchymal type and certainly not characteristic of simple obstructive jaundice. Operative intervention was deferred and the patient was transferred to the medical service Oct. 10. In the next ten days, jaundice increased greatly, the serum bilirubin reaching a maximum of 27.6 mg. per 100 cc. Cephalin cholesterol flocculation test was markedly positive. There was a high degree of exclusion of urobilinogen from the gastrointestinal tract, and a relative increase in the amount of urobilinogen being excreted in the urine. The patient's clinical condition remained static; at no time did he appear to be acutely ill. Duodenal drainage with magnesium sulfate was undertaken three times without avail. Because of the difficulty in differential diagnosis, a biopsy specimen was taken from the liver. The pathological report was as follows:

Microscopic: Section showed a mild portal infiltration chiefly by mononuclear leukocytes with scattered eosinophils and polymorphonuclear leukocytes. There was no increase in portal connective tissue and no bile duct proliferation. The liver cord cells surrounding the central vein were swollen and pigmented. Many of the reticuloendothelial cells along the sinusoids contained bile pigment. Bile capillary thrombi were numerous particularly in the central zone. A few scattered degenerating liver cord cells were noted and there were a few regenerative forms.

Comment: A number of pathologists reviewed the slide and, although there was some divergence of opinion, the majority interpreted the findings as consistent with obstructive jaundice.

About Oct. 20 the jaundice began to diminish. Coincidentally, there was pronounced and rapid increase in the rate of excretion of urobilinogen in the feces, and by Oct. 25 it had reached 192 Ehrlich units per 100 gm. Urinary excretion of urobilinogen, which previously had been at a rate of 1 mg. per day, reached 42 mg. per day. There was considerable decrease in the serum bilirubin to a total of 7.9 mg. per day at the time of discharge. It was thought that the extent of increase in the fecal urobilinogen was more in line with resolving hepatitis than with extrahepatic obstruction due to stone. The results of the liver biopsy, although favoring obstructive jaundice, were still somewhat equivocal. The patient was discharged Oct. 25 to return to his home.

The patient remained well with no jaundice or other symptoms. The final diagnosis was homologous serum hepatitis.

CASE 2: The patient, a woman 22 years of age, had had cholecystectomy with common duct drainage on Jan. 31, 1948, at St. John's Hospital in Santa Monica. Postoperatively the patient received 500 cc. of pooled plasma and 30 cc. of human albumin to overcome a depression of blood pressure. Convalescence was uneventful and the patient was discharged from the hospital on Feb. 11, 1948. The T-tube was removed on March 5 after it had been clamped for a week when cholangiogram showed no further obstruction or stones. Sixty days after operation there was onset of anorexia and nausea with upper abdominal distress, fever, dark urine and light stools. The icteric index was 23 units. Leukocytes numbered 6,350. Jaundice was observed clinically. The liver edge was palpated two finger-breadths

below the right costal margin and was tender. The thymol turbidity test reached 19 units. Bile was present in the urine. No other tests of liver function were done at the time as it was the impression of the medical consultant that the patient had homologous serum hepatitis. After three weeks of high-protein, high-carbohydrate, high-vitamin diet and bed rest, the patient made good recovery and resumed full normal activity in six weeks. The liver was no longer enlarged or tender. Cephalin cholesterol flocculation was normal. The patient remained well.

CASE 3: A white male, 63 years of age, was admitted Oct. 1, 1946, to Cedars of Lebanon Hospital with a history of pain in the right upper quadrant of the abdomen, recurrent nausea, vomiting and jaundice. The admission diagnosis was acute cholecystitis, common duct stone with obstructive jaundice. There was tenderness in the right upper quadrant of the abdomen. The gallbladder was palpable. The icteric index was 34 units. The patient was prepared for cholecystectomy. On Oct. 9, there was a severe reaction to amino acid solution given intravenously. The patient went into a state of deep shock and collapse for which 500 cc. of pooled plasma was given. On Oct. 12 a blood transfusion (individual donor) was given because of anemia. The hemoglobin, which was normal before the protein reaction, had dropped to a value of 50 per cent. On Oct. 22, the gallbladder, full of small stones, was removed. The common bile duct was opened and gravel was removed. A cholangiogram taken during the operation showed no further obstruction and a T-tube was inserted into the common duct. The patient was given 500 cc. of whole blood (individual donor) during the operation. The postoperative course was uneventful. The T-tube was clamped for one week. A cholangiogram on Oct. 31 showed no abnormality. The patient noted onset of painless jaundice on Feb. 11, the 112th day following operation. The stools were normal in color at first and then became acholic. The urine was dark. The liver was tender and palpable, and the spleen was palpable 3 cm. below the costal margin. Jaundice deepened rapidly until the icteric index reached 300 units. On Feb. 19 the icterus began to subside. On Feb. 13 the icteric index had been 267 units; on Feb. 21 it was 95 units. The patient had been treated with bed rest, high-protein diet, glucose administered intravenously, vitamin K, choline, methionine and vitamin B complex. Discharged Feb. 22, the patient remained well.

SUMMARY

Cases of homologous serum hepatitis may be overlooked because the condition is not usually considered in the differential diagnosis of jaundice. It is essential that it be suspected particularly if there is a history of illness or an operation requiring transfusion of blood or plasma two to five months before the development of jaundice, even if the operation was performed upon the biliary tract. This suspicion may be confirmed by demonstration of positive signs of hepatocellular jaundice by liver function tests. The indiscriminate use of pooled plasma is to be condemned because of the hazard of homologous serum hepatitis.

Three cases have been presented to illustrate that recurrent jaundice after biliary tract operation may be due to homologous serum hepatitis.

405 North Bedford Drive.

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Electrocardiogram Immediately Before and After Septal Infarction

Report of a Case

A. B. BIGLER, M.D., *Chowchilla*

THE following case report is presented to illustrate graphically two recently published statements. The first is from the University of Oregon Medical School syllabus on Electrocardiography,[1] soon to be published as a textbook: "Coronary disease may also exist in the complete absence of electrocardiographic abnormalities." The second is from an article by Gordon Myers and co-workers:[2] "Little or no attention has been devoted to the diagnosis of septal infarction in the current textbooks and monographs on electrocardiography."

The authors of both statements report cases in which the diagnosis was proven by autopsy, showing that right bundle-branch block due to septal infarction was differentiated from that due to other causes by the direction of the initial phase of the QRS complexes in leads from the right precordium. Uncomplicated right bundle-branch block was manifested by an initial R wave, a subsequent downstroke or coarse blurring, and a secondary late upstroke, whereas right bundle-branch block associated with septal infarction was characterized by an abnormal Q wave and a later R wave in these leads.

CASE REPORT

The patient, a 47-year-old male turkey-grower, was first observed on the afternoon of May 31, 1949. The present illness had begun two months previously with onset of indigestion. Any food caused indigestion. There had been no pain in the chest, but pain in the arm, running down to fingers, was a frequent occurrence. The patient took baking soda habitually for relief, with seeming success. He said that when mowing the lawn he had to stop and rest frequently because of pains in both shoulders. On the day he was first observed, repeated attacks of indigestion had occurred since morning, and with them for the first time there was pain in the chest. Stooping over to pick up baby turkeys would initiate a spell.

The patient was well-nourished, and appeared to be about the stated age. He was in no apparent distress. Heart sounds were regular and not otherwise abnormal. The blood pressure was 130 mm. of mercury systolic and 80 diastolic. An electrocardiogram tracing (Figure 1, *a*), taken about 4 p.m., was considered to be normal.

A prescription was given for nitroglycerin tablets, 0.3 mg., to be taken as a therapeutic test for the spells. The patient was told to return next morning to report. It was intended at that time to attempt to reproduce the pain and take further tracings.

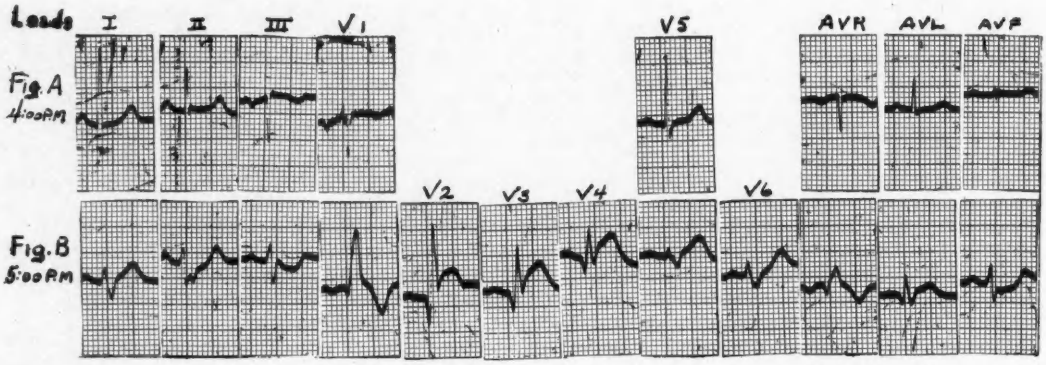

Figure 1.—*Top strip:* Electrocardiogram considered normal. The left axis deviation could be accounted for by the horizontal position as shown by AVL resembling V_5. V_1 is shown to demonstrate the presence of an initial R wave in the right ventricular lead.

Bottom strip: Electrocardiogram taken one hour later. The main consideration is the sudden appearance of right bundle-branch block, with the disappearance of the early R wave in V_1 and its replacement by a Q wave. Lead V_1 now shows a tall late R wave and an intrinsicoid deflection beginning 0.1 second after the beginning of the QRS complex, whereas lead V_6 shows the R wave to have an intrinsicoid deflection of about 0.02 second followed by a broad slurred S wave.

The changes shown are characteristic of right bundle-branch block. The early R wave in V_1 (*top strip*) is a normal wave produced by early left-to-right activation of the septum. Its disappearance and replacement by a Q wave therefore constitutes evidence of infarction of the septum. The initial Q wave in V_1 (*bottom strip*) represents a left ventricular cavity potential transmitted through an inert septum. According to Myers[2] the tall late R wave (V_1, *lower strip*) is "derived presumably from activation of an uninfarcted outer wall of the right ventricle over the aberrant pathway." The abnormal Q waves and RS-T displacements in leads V_3 and V_4 indicate continuation of the septal infarct into the anterior wall of the left apex.

Twenty minutes later, the patient was assisted back to the office with excruciating substernal and arm pain obviously overshadowing any previous attack. The attack had occurred in a drug store, and as two tablets of nitroglycerin gave no relief, he was brought back to the office by car. Forty-five milligrams of morphine sulfate—including 15 mg. intravenously—was required to subdue the pain appreciably.

From an electrocardiogram (Figure 1, *b*) taken an hour after the first one, it was at once apparent that pronounced myocardial insult had suddenly occurred.

The patient rapidly went into cardiac failure, but maintained a vegetative existence for two weeks with constant supplemental oxygen. No autopsy was obtained.

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Tuberculous Fistula in a Postpartum Uterus

Report of a Case

CHESTER L. ROBERTS, M.D., *Glendale*

IN a careful survey of the literature no previous report of a case of tuberculous fistula of the uterus was found. There are scattered reports of tuberculous endometritis, but in only rare instances was this disease not accompanied by tuberculosis elsewhere in the body. The case of tuberculous endometritis, complicated by fistula formation, here reported, appears to be the first in medical literature.

CASE REPORT

A 22-year-old gravida II, para I, was observed Oct. 21, 1946, in early pregnancy. The date of last menses was Aug. 10. The previous child had been delivered June 4, 1946. Except that the patient had a left inguinal hernia for which a truss was worn intermittently, the first prenatal course, delivery and postpartum period were without unusual incident.

Results of an examination were normal and the hernia was not palpable. At no time during the prenatal course was the temperature elevated, except for a day in Jan. 1947, when the patient had a cold. Records of the Los Angeles County General Hospital where the patient was sent for delivery showed that labor began without inducement on May 25, 1947, and within three hours the baby was delivered spontaneously. The placenta apparently was completely delivered. The postpartum course was somewhat febrile, with temperature ranging between 99° F. and 102° F. Penicillin was given. However, fever and night sweats were present during the entire stay in the hospital. The patient was dismissed on the fifth postpartum day. An intern reported that the uterus was involuting normally, being three finger-breadths below the umbilicus, but that there was generalized abdominal tenderness. The lungs were reported clear to auscultation.

On June 12, 1947, 17 days postpartum, the patient again consulted the author with complaint that the uterus had not gone down at all and that she felt that there must be another baby present. At that time the temperature was 103° F., and the patient stated that it had been elevated since she had been at home and that night sweats had become progressively worse from the time she left the hospital.

Upon examination it was noted that the uterus extended above the umbilicus. Attached the uterus and extending to within 3 cm. of the xiphoid process was a firm, trough-like mass in the midline. It was about 8 cm. wide and was attached to the anterior abdominal wall. A diagnosis of metritis with possible rupture of the uterus was made. At that time it was believed that the trough-like mass was omentum, attempting to wall off a rupture site in the uterus.

The patient was hospitalized and a diagnostic dilatation and curettage done. The curette passed up beyond the fundus of the uterus into this trough-like process and could be felt under the skin, 3 cm. below the xiphoid process. Curettings gently taken from this area and from the uterus revealed tuberculosis. X-ray films of the chest revealed fluid in the base of the left lung and the patient was returned to the Los Angeles County General Hospital. Sputum specimens examined there were never positive for tubercle bacilli.

An extremely febrile course followed and the patient was given streptomycin. By Aug. 1, 1947, the mass was no longer palpable. On Aug. 25, exploratory laparotomy was done. Inoperable tuberculous peritonitis was found. The pelvis was so infiltrated with tubercles that none of the organs except a small portion of the right tube were recognizable. A plaque 8 cm. wide and 1 cm. thick extended from the bladder to above the umbilicus. The peritoneum was studded with granules. Two hundred cc. of straw-colored fluid was removed and a biopsy specimen of the tuberculous tissues was taken. Streptomycin was continued postoperatively. The abdominal wound healed without incident and the patient was discharged Sept. 18, 1947.

Follow-up x-ray films of the chest have shown no abnormality. The mass up the midline of the abdomen is gone entirely. Menstrual periods have been normal. The patient is active and has no discomfort.

About July 1, 1947, while the patient was in the hospital, her year-old son was also admitted and, in spite of streptomycin therapy, died of tuberculous meningitis Dec. 16, 1947. The remaining child and the patient's husband are living and well.

The tuberculous endometritis was undoubtedly present during the pregnancy and the diseased myometrium ruptured during labor. The omentum, in its attempt to wall off the area, formed the walls of the fistula which, fortunately, never became a draining sinus. With streptomycin, the active spread of the endometritis was halted and spontaneous regression occurred. Thus, the fistula probably was a direct result of the rupture of a tuberculous uterus during labor.

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EDITORIAL

The Hess Report and What It Means

In 1948 a committee of the House of Delegates of the American Medical Association was given the duty of studying the problem and status of "Hospitals and the Practice of Medicine." The chairman of this special committee was Dr. Elmer Hess of Erie, Pennsylvania. Hence, it became known as the Hess Committee and its reports of various times became known as the Hess Reports.

The progress report given to the House of Delegates at St. Louis in December 1948 merely outlined some principles and ways by which the committee would seek facts to enable it to render an opinion.

In June 1949, at Atlantic City, Dr. Hess reported for the committee.

He called attention to the fact that in many or most states the practice of medicine by corporations or unlicensed individuals is illegal. He also called attention to the Principles of Ethics of the American Medical Association (Chapter II, Article VI, Section 6) wherein the disposal by a physician of his services to such a party, where there is exploitation of the physician's services for the financial profit of such agency, is declared unethical. "Therefore," Dr. Hess stated in the report, "hospitals and medical schools cannot charge patients fees for medical services rendered by physicians even though the physicians are full time employees of an individual or of an institution."

Dr. Hess pointed out that these basic principles should be definitely understood and confirmed. Then he recommended that hospitals or other lay groups that would not cooperate within ethical and legal limits, and had been found guilty, should be removed from the approval list of the American Medical Association on order of the Judicial Council. This is the point on which much later misunderstanding arose.

The Reference Committee of the House of Delegates recommended approval of this "Hess report" and it was so approved.

Thereafter the Board of Trustees was given legal advice that the board had no right legally to try hospitals or other lay groups as to their lack of cooperation. Also, that as the American Medical Association had no legal authority to state how hospitals should carry on their business, the American Medical Association could not legally carry out this provision of the Hess report. The Board of Trustees therefore refused to institute any action and asked the House of Delegates to rescind its action approving the Hess report.

Therefore, at Washington in December 1949, the House of Delegates reconsidered the whole problem, but refused to rescind the Hess principles and pointedly reaffirmed its belief in those principles stated in the Hess report, and directed that action by the Board of Trustees be deferred *only* until all legal requirements were met in order to insure that all action taken should comply with the law.

Thereafter, the American Hospital Association in March 1950, in a distributed brochure, quoted resolutions defining that in its opinion radiologic, pathologic, anesthesiologic and psychiatric departments are component parts of the hospital organization and are included properly in a "patient-day" of hospital care. It definitely branded certain designated branches of medicine as hospital functions rather than professional medical care functions. It also erroneously reported that the Hess report had been rescinded.

This apparently caused much unrest and resentment in many quarters and it was felt that definite unequivocal action had to be taken by the House of Delegates in San Francisco.

In June 1950, therefore, the final (to date) Hess report was presented to the House of Delegates. It was then referred to a Resolutions Committee for study and report. Open hearings were held by this committee and its recommendations made. The House of Delegates then acted and this is essentially what it adopted:

1. It reaffirmed the basic principles of the Hess report in separating professional services from those which are the functions of the hospitals.

2. It called attention to procedures by which legally a physician (not the hospitals) may be tried for unethical conduct.

3. It adopted the following: "If and when a physician is found to be unethical by the proper authorities as established through channels specified in the Constitution and By-Laws, and he is still retained on the staff of any hospital approved for resident or intern training by the Council on Medical Education and Hospitals, it shall be the duty of the Judicial Council to request the Council on Medical Education and Hospitals to show cause as to why that council should not remove such hospital from the approved list under the assumption that the hospital is just as unfit for the training of young physicians for unethical reasons as it is unfit because it may not or does not have proper filing systems for its laboratory or clinical records."

4. It stated:

a. "A physician should not dispose of his professional attainments or services to any hospital, corporation or lay body by whatever name called or however organized under terms or conditions which permit the sale of the services of that physician by such agency for a fee.

b. "Where a hospital is not selling the services of a physician, the financial arrangement, if any, between the hospital and the physician properly may be placed upon any mutually satisfactory basis. This refers to the remuneration of a physician for teaching or research or charitable services or the like. Corporations or other lay bodies properly may provide such services and employ or otherwise engage doctors for those purposes.

c. "The practice of anesthesiology, pathology, physical medicine and roentgenology are an integral part of the practice of medicine in the same category as the practice of surgery, internal medicine or any other designated field of medicine."

Undoubtedly it will take time to adjust all difficulties. However, the basic principles in this problem have been enunciated and the procedures necessary to support them are described.

Honorable bodies given definite precepts and rules of conduct usually adjust themselves and embrace the right.

CALIFORNIA MEDICAL ASSOCIATION

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NOTICES AND REPORTS

Executive Committee Minutes

Tentative Draft: Minutes of the 222nd Meeting of the Executive Committee, San Francisco, June 15, 1950.

The meeting was called to order by Chairman Donald D. Lum in Room 212 of the St. Francis Hotel, San Francisco, on Thursday, June 15, 1950, at 3:00 p.m.

Roll Call:

Present were President Cass, President-elect MacLean, Speaker Alesen, Council Chairman Shipman, Auditing Committee Chairman Lum and Editor Wilbur. A quorum present and acting. Present by invitation were Executive Secretary Hunton, Assistant Executive Secretary Wheeler, Legal Counsel Hassard and Mr. Clem Whitaker, Jr., of public relations counsel.

1. *Time and Place of Interim Session, House of Delegates:*

After discussion, it was regularly moved, seconded and voted that the interim session of the House of Delegates, voted by the Council at its meeting of May 27, 1950, be held on December 2 and 3, 1950, in Sacramento.

2. *Nominations for Secretary-Treasurer:*

It was regularly moved, seconded and voted that Dr. M. Laurence Montgomery be named Assistant Secretary-Treasurer, in compliance with action of the Council, to serve during the interim prior to appointment of a Secretary-Treasurer.

It was regularly moved, seconded and voted that Dr. Albert C. Daniels of San Francisco be nominated to the Council for appointment as Secretary-Treasurer.

3. *San Diego Blood Bank:*

Discussion was held on the San Diego Blood Bank and the possible advance of loan funds for conversion of this bank to a community-type blood bank as a part of the statewide system. Pending receipt of further information of the conditions in the existing blood bank, no action was taken.

4. *Public Policy and Legislation:*

It was regularly moved, seconded and voted that assistance and cooperation be given to the Los Angeles physicians who are combating a proposed antivivisection initiative in that county.

After discussion of various matters, it was regularly moved, seconded and voted to appropriate up to $15,000 additional funds to the Committee on Public Policy and Legislation to meet the approved requirements of that committee.

5. *National Society for Medical Research:*

On motion duly made and seconded, it was voted to continue the contribution of $500 for the coming year to the National Society for Medical Research.

6. *Resolutions to House of Delegates:*

Discussion was held on the position of the Council with regard to offering possible amendments to actions taken at the 1950 House of Delegates on oaths of office required of officers, employees and members of the House of Delegates. It was agreed to poll the members of the Council to solicit their suggestions for this and other matters to be placed on the agenda of the interim meeting of the House of Delegates.

7. *Publication of Tuberculosis Papers:*

A request from the California Tuberculosis & Health Association for authority to publish papers from its annual meeting as a supplement to CALIFORNIA MEDICINE was discussed and it was regularly moved, seconded and voted to leave such publication at the discretion of the Editor and the Editorial Board.

8. *American Legion, California Department:*

A request from the American Legion, California Department, for physicians to observe certain practices in treating veterans whose cases might come within the scope of the Veterans Administration, was discussed. It was pointed out that California Physicians' Service has already brought this matter to the attention of its professional members and it was ordered that the American Legion be so notified.

9. *Hawaii Tour Tickets:*

The Executive Secretary asked for instructions for the distribution of airline transportation accom-

modations to Hawaii which have come to the Association through its sponsorship of an organized tour. On motion duly made and seconded, it was voted to offer these tickets to employees in the Association office.

10. *Better Business Bureau of San Francisco:*

On motion duly made and seconded, it was voted to contribute $25 to the Better Business Bureau of San Francisco as a gesture of appreciation for its cooperation.

11. *Expenses of County Society Executive Secretaries:*

The Executive Secretary reported on the cost of travel and other expenses of county society executive secretaries in attending Council meetings, in response to a request made following the May 27 Council meeting. Transportation costs for nine county society executive secretaries were reported to total from $192 to $232, depending on the location of the meeting. It was regularly moved, seconded and voted that the Association bear the expenses of these county representatives to regular committee meetings scheduled in advance of Council meetings but that additional costs for attendance at Council meetings be an obligation of the county societies.

12. *Council Minutes:*

The Executive Secretary reported that amendments had been proposed for Minute No. 28 of the Council meeting of May 27, 1950. On motion duly made and seconded, it was voted to approve an amendment to this minute prior to its publication in CALIFORNIA MEDICINE.

13. *Committee on Advertising:*

Discussion was held on the advisability of accepting certain types of advertising in the journal which might be in conflict with the policies of the Association. It was agreed that a member of the Council be invited to sit with the Committee on Advertising to advise the committee when such matters were before it.

14. *Legal Department:*

Mr. Hassard discussed several items and suggested the advisability of exploring the educational standards of several of the healing arts. It was regularly moved, seconded and voted to authorize legal counsel to look into the educational provisions of chartered schools offering medical or ancillary courses.

15. *World Medical Association:*

It was regularly moved, seconded and voted to request Dr. John W. Cline, A.M.A. representative to the World Medical Association, to represent the California Medical Association at the next annual meeting of W.M.A.

16. *Chamber of Commerce of the United States:*

A request from the Chamber of Commerce of the United States to take out a membership in that body was discussed and ordered referred to the American Medical Association.

17. *Sectarian Medicine:*

A request from a county medical society as to whether or not the practice of homeopathic medicine and holding oneself out to be a homeopath constituted sectarian medical practice in violation of county society by-laws prohibiting such practice, was discussed. It was agreed that the practice of homeopathic medicine in itself did not constitute sectarian practice but that in the instance before the committee, the county society should be advised to exercise its own judgment as to the ethical nature of the telephone book listings of the present applicant.

18. *C.M.A. Mailing List:*

It was regularly moved, seconded and voted to permit the California Heart Association to use the mailing list to send programs of its meeting to C.M.A. members.

19. *Committee on Emergency Medical Service:*

It was regularly moved, seconded and voted to recommend to the Council the appointment of Dr. Frank F. Schade of Los Angeles as an additional member of the Committee on Emergency Medical Service.

20. *Medical School Clinical Material:*

Discussion was held on the question raised by medical school deans as to the acceptance on the basis of pathology of selected members of prepayment plans, to come into the clinical wards of teaching hospitals rather than as private patients. It was regularly moved, seconded and voted that the Council Chairman appoint a committee to meet with representatives of the medical deans to work toward a solution of this problem.

21. *"Future M.D.":*

It was regularly moved, seconded and voted that CALIFORNIA MEDICINE be sent to all medical students, interns and residents if postal regulations would permit. It was also agreed to recommend to the Council that all publications of the Association be subject to final edit by the Editor (with the advice and assistance of the Editorial Board), pursuant to the provisions of Section 8 of Chapter 6 of the By-Laws.

Adjournment:

There being no further business to come before it, the meeting was adjourned at 7:00 p.m.

DONALD D. LUM, M.D., *Chairman*
M. LAURENCE MONTGOMERY, M.D.
Assistant Secretary-Treasurer

Postgraduate Activities in Los Angeles County

The following report was prepared by Dr. Charles A. Broaddus, California Medical Association Director of Postgraduate Activities, who plans to make further reports from time to time as information is assembled, as a means of stimulating the organization of postgraduate education programs by county societies and other local groups.

The Los Angeles County Medical Association does not have general meetings for postgraduate educational programs. The general practice section and the various specialty groups are so large that each has its own separate program.

This year an effort is being made to put special emphasis on the subject of tumor growths by having each section of the county association put on two programs devoted entirely to cancer in the field of its specialty.

In addition to the frequent meetings of all the specialty groups which keep the association's auditorium occupied every night in the week, there are other special meetings which deserve attention.

Early this year the county association put on an outstanding chest symposium for the general practice section. This was prepared by a committee under the leadership of Dr. L. C. Burwell. A registration fee of $5.00 was charged for the two-day session. The program included the following:

"The Differential Diagnosis of Cough," Dr. Daniel Myers, Wayne University Medical School.

"What to Know About Carcinoma of the Lung," Dr. Robert M. James, University of Toronto Medical School.

In addition, many subjects relative to diseases of the chest were discussed by several physicians including Drs. Gordon Meiklejohn, H. Corwin Hinshaw, Charles Edward Smith, and R. R. Newell, all of San Francisco; Rutherford T. Johnstone, Robert J. Anderson, George Griffith, Roger Egeberg, Francis Byron and Howard Bosworth of Los Angeles; and Edward Kupka of Berkeley.

A unique group in the San Fernando Branch is known as the "Doctors' Breakfast Club" which meets every Wednesday at 7:30 a.m. in the dining room of St. Joseph's Hospital. This group was organized three years ago with a membership of seven doctors led by Dr. David Lindemauer, chairman. The membership has steadily grown until now there are a hundred or more in attendance. No dues are charged. The program is arranged and printed six months in advance. Speakers are limited to 35 to 40 minutes for lecture and allowed 15 to 20 minutes for a question period. No honorarium is paid. Occasionally, as opportunity presents, a famous physician from out-of-state may be introduced or substituted for the regular speaker. In the past three years the group has met weekly without fail.

A similar group of 55 physicians has formed a "Doctors' Breakfast Club" which has been meeting weekly in the eastern part of Los Angeles County at the Murphy Memorial Hospital of Whittier. This group has grown up during the past 18 months under the leadership of Dr. Walter Wilson.

Plans are being made to form other such breakfast clubs in various part of the county.

The Research Study Club of Los Angeles is another organization successfully promoting postgraduate education. Earlier this year it completed its 19th annual clinical convention in ophthalmology and otolaryngology with an attendance of 400 from all over the United States, Canada, Hawaii and Mexico. Among the lecturers present were Dr. Conrad Berens and Dr. Raymond E. Meek of New York City and Dr. Percy E. Ireland and Dr. Joseph A. Sullivan of Toronto, Canada.

Valley Blood Bank

A vital link to the blood bank service in California has been the addition of the Valley Blood Bank of Fresno, California. Its location in the geographical center of California is an important step in connecting the growing blood bank centers already established in Southern and Northern California.

Its origin on December 1, 1948, was effected through the combined efforts of the Fresno County Medical Society and Dr. J. R. Upton, chairman of the California Medical Association Blood Banks Commission. Up to the time of the Valley Blood Bank operation, the major part of the San Joaquin Valley had been supplied with blood by the Fresno County Hospital. With the increasing demand for blood in this area, Fresno physicians and Dr. Upton realized the necessity for establishing a separately organized blood bank service. At a meeting of the Fresno County Medical Society late in 1948 positive steps in this direction were outlined. The society sanctioned the establishment of a bank to be called the Valley Blood Bank under the direction of C. D. Newel, M.D. The bank began operation on December 1, 1948.

Operating with its center in Fresno, the Valley Blood Bank has grown during its first year by serving Madera, Kings, Merced, Mariposa, and Tulare counties in addition to Fresno County. In order to provide an adequate blood supply to this total area (17,801 square miles) mobile blood drawing units were necessary. Through the cooperation of various hospital officials in the valley, a mobile drawing unit was organized, and now draws weekly at hospitals in Merced, Madera, Hanford, and Tulare. The latest addition in the growing list of hospitals to use the service of the Valley Blood Bank is the recently completed 250-bed Veterans Hospital located in Fresno.

In the first year of operation 6,000 donors gave blood; 85 per cent of it was used for whole blood transfusions and the remaining 15 per cent was dispensed through processing for plasma.

The Valley Blood Bank operates essentially as do the Sonoma, Alameda, San Mateo and Irwin Memorial blood banks. The usual maintenance service fee is charged to the patient in order to cover the cost

of drawing the blood, processing and dispensing it, and replacement is required. This basic axiom guarantees a constant supply of blood and prompt service to the numerous hospitals using the blood bank facilities.

Several valley organizations have set up credits for themselves and their families. Among these are listed:

State Highway Patrol.

Communication Workers of America.

Pacific Gas and Electric Company of the San Joaquin Valley.

Navy Club of Fresno.

The Lemoore Eagles.

Eastern Star division of Fresno and Mariposa counties.

Other groups have expressed a desire to establish credits with the Fresno bank and they will be cared for.

A favorable commentary on its effectiveness in contributing to the health of the valley community is the fact that outlying valley hospitals are actively responding to the formation of subsidiary blood bank depots. With the establishment of these emergency depots, the more isolated communities are guaranteed faster blood delivery.

In Memoriam

CHING, MARCUS. Died in San Francisco, June 14, 1950, aged 38, of carcinoma of the pancreas. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1937. Licensed in California in 1938. Dr. Ching was a member of the Santa Clara County Medical Society, the California Medical Association, and the American Medical Association.

✤

HAYHURST, WENDELL O. Died in Burbank, May 3, 1950, aged 40. Graduate of Baylor University College of Medicine, Houston, 1932. Licensed in California in 1936. Dr. Hayhurst was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

MYERS, GLENN E. Died in Los Angeles, June 11, 1950, aged 64. Graduate of the Indiana University School of Medicine, Bloomington-Indianapolis, 1909. Licensed in California in 1916. Dr. Myers was a member of the Los Angeles County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

SCHENCK, GEORGE F. Died in Los Angeles, June 5, 1950, aged 59, of a coronary. Graduate of the College of Physicians and Surgeons, Los Angeles, 1917. Licensed in California in 1917. Dr. Schenk was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

SHUFELT, ALSON A. Died in San Jose, June 11, 1950, aged 58, of a coronary. Graduate of the University of California Medical School, Berkeley-San Francisco, 1917. Licensed in California in 1917. Dr. Shufelt was a member of the Santa Clara County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

✤

SINGER, HARRY. Died in Los Angeles, June 8, 1950, aged 51, of a heart attack. Graduate of the University of Illinois College of Medicine, Chicago, 1925. Licensed in California in 1926. Dr. Singer was a member of the Los Angeles County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

SNOW, WILLIAM F. Died in Bangor, Maine, June 12, 1950, aged 75. Graduate of the Cooper Medical College, San Francisco, 1900. Licensed in California in 1900. Dr. Snow was a retired member of the Santa Clara County Medical Society, and the California Medical Association.

✤

SPALDING, WILLIAM C. Died in Hillsboro, Texas, May 23, 1950, aged 60, from angina following a coronary. Graduate of the College of Physicians and Surgeons of Baltimore, 1915. Licensed in California in 1922. Dr. Spalding was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

WILSON, KENNETH G. Died in Laguna Beach, June 20, 1950, aged 35. Graduate of the University of Minnesota Medical School, Minneapolis, 1941. Licensed in California in 1945. Dr. Wilson was a member of the Orange County Medical Society, the California Medical Association, and the American Medical Association.

Questions and Answers about C. P. S.

If you have a question of general interest about C.P.S., please address it to the editor of CALIFORNIA MEDICINE.

Question: **Until the recent introduction of the revised Billing Form 9, I have found the itemization of my payments on a small white printed form attached to my returned claim. Where do I find this information now that the new Form 9 is being used?**

Answer: This small white form has been abolished for claims submitted on the new Form 9. The breakdown of payments now appears on Part 3 of the revised form. This change was made because it reduced clerical work in C.P.S. offices, thus effecting financial savings.

Question: **Where several different types of services are paid on one claim, how do I determine how much has been paid for each service?**

Answer: Refer to Part 3 of the new Billing Form 9 under the column headed "Proc" (for Procedure). The numbers listed there, and the payments shown opposite, correspond to procedures listed in the fee schedule.

Question: **What has been the experience with regard to "catastrophic coverage," the new protection against the costs of 23 major ailments?**

Answer: Benefits of the catastrophic plan were first offered to Northern California residents on February 1, 1950, and to Southern California residents on March 1. In the few months since then more than 5,000 beneficiary-members have availed themselves of this additional protection.

Thus far, only a comparative handful of claims have been paid, and the true experience of catastrophic coverage must await a considerably longer lapse of time. Meanwhile, the C.P.S. administration is progressing carefully with this new protection, and health statements are required for all applicants.

Question: **Last April I received a letter from the C.P.S. Veterans' Department informing me that, due to a shortage of government funds, authorizations to treat veterans under the Home Town Care Program would be limited by the Veterans' Administration. Does this shortage of funds continue into the new Federal fiscal year which started July 1?**

Answer: No. Since July 1 authorizations for treating veterans have not been limited because of a shortage of funds. A new appropriation has become available and authorizations are being issued in the usual manner.

Question: **For purposes of the Veterans' Program, does the term "service-connected" mean a condition for which the veteran was hospitalized or treated during the period he served in the military forces?**

Answer: No. "Service-connected" means that the veteran has been legally rated by an Adjudication Board of the Veterans Administration for a specific condition (or conditions) which was service-incurred or aggravated. According to law, the veteran is thereby entitled to treatment for that condition at government expense.

Question: **If a changed condition develops in one of my veteran patients, how can I obtain approval to render the additional services which become necessary — and which were not included in my original monthly authorization?**

Answer: Once you have received your monthly authorization for treating a veteran patient, authorization for additional services may be requested by telephone or letter. In an emergency, telephone the C.P.S. Veterans' Department in San Francisco, Los Angeles or San Diego. In other cases, send a letter—but do not render any of the additional services until the supplemental authorization has been received.

Question: **What is the latest date I can submit my bill to C.P.S. and still receive payment the following month?**

Answer: To be paid in the following month, bills should be received by C.P.S. on or before the 15th of the month. For example: June bills received by C.P.S. on or before July 15 normally are paid in the early part of August. However, if a bill does not properly identify the patient and/or the physician, or if more information is required regarding the service rendered, processing of the claim is delayed pending clarification.

Question: **Can I phone C.P.S. for quick information about the benefits to which a specific C.P.S. patient is entitled?**

Answer: Yes, call the Inquiry Section of the Medical Department in San Francisco or Los Angeles. Be sure to give the patient's name, membership number (and code numbers, if available), and relationship to the subscriber-member — e.g., son, daughter, wife or husband.

Question: **I have had my bill returned with the following statement stamped across the front: "We cannot identify your patient as a beneficiary member of C.P.S. under the above certificate number." Does this mean the person is not a C.P.S. member?**

Answer: Not necessarily. It is more likely that the member's correct C.P.S. number has not been shown on the bill. Many bills are received with incorrect numbers—and sometimes with no number.

NEWS and NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

Physicians in the Los Angeles area have been asked to notify the City Health Department by phone of possible or **suspected cases of Q fever** coming to their attention in order that the patients may be subjected to a new diagnostic test for the disease.

Studies of the new test, which may be applicable in the acute as well as in the convalescent stage of the disease, are being conducted by Dr. Joseph Victor of the U. S. Public Health Service as a part of the continuing research on Q fever in the Los Angeles area.

In addition to notifying the City Health Department, physicians are requested to obtain a specimen of blood which will be collected by the health department for complement fixation tests. The department then will contact the physician with regard to follow-up for additional blood specimens for special diagnostic studies by Dr. Victor in suitable cases.

ORANGE

Dr. Joseph Preizler has been appointed Orange County deputy health officer in charge of tuberculosis control. He succeeds Dr. Erwin P. Brauner who resigned to take appointment as health commissioner for the American zone of Berlin.

SAN FRANCISCO

Dr. Robert A. Scarborough of San Francisco was elected president-elect of the American Proctologic Society at the recent convention of that organization in Los Angeles.

* * *

Three awards totaling $55,580 for **studies of poliomyelitis** were made to the University of California by the National Foundation for Poliomyelitis in June. The largest, a grant of $41,580, was allocated for virus research under the direction of Dr. Wendell M. Stanley. A grant of $4,900 was made for support of studies on the blood brain barrier in relation to poliomyelitis under the direction of Dr. Robert B. Aird, and $9,100 was allotted for studies on treatment under the direction of Dr. LeRoy C. Abbott.

* * *

Renewal of National Cancer Institute grants to two California teaching institutions to aid in improved **training of students with regard to cancer** was approved recently by Dr. Leonard A. Scheele, surgeon general of the U. S. Public Health Service. Stanford University School of Medicine was allotted $21,958 and the University of California Dental School $4,968.

GENERAL

Applications for **American Heart Association research fellowships** and stipends for established investigators will be accepted up to September 15, 1950, according to an announcement by Dr. Howard B. Sprague, president of the association. Applications for research grants-in-aid, including grants for research in basic sciences not necessarily directly related to cardiovascular disease, may be filed up to December 15. More than $1,000,000 will be allotted this year by the American Heart Association and is affiliates, it was announced.

Fellowships for established investigators may be granted for a five-year period at a minimum stipend of $5,000, with an annual increase of $500. "They are open to superior individuals of proven originality, with the degrees of Doctor of Medicine, Doctor of Philosophy, or Doctor of Science, or equivalent degree, who are interested in making a career in research," the announcement said.

Eligible for research fellowships, which are granted for a one-year period with a stipend ranging from $3,000 to $4,300, are graduates of approved medical or graduate schools who are interested in research and intend to follow an academic career.

* * *

The American Roentgen Ray Society will hold its 50th anniversary meeting in St. Louis, September 26-29.

* * *

The International College of Surgeons, United States Chapter, will hold its 15th Annual Assembly and Convocation in Cleveland, Ohio, October 31, November 1, 2, 3, 1950. All doctors of medicine interested in surgery and its advancement are invited to attend, and can obtain a program upon request to Arnold S. Jackson, M.D., Jackson Clinic, Madison, 4, Wis.

* * *

Community blood banks in California are prepared for full cooperation with defense planning, Dr. John R. Upton, chairman of the California Medical Association's Blood Bank Commission, notified the Office of the Secretary of Defense last month. The facilities of the various community blood banks in the state was offered for use in procurement and processing of **blood for overseas shipment.**

* * *

The American Urological Association recently announced its annual award of $1,000 (first prize of $500, second prize of $300 and third prize $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to men in training to become urologists. The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Palmer House, Chicago, Illinois, May 21-24, 1951.

Full particulars may be obtained from the secretary of the association, Dr. Charles H. de T. Shivers, Boardwalk National Arcade Building, Atlantic City, New Jersey. Essays must be in his hands before February 10, 1951.

* * *

Two medical committees to formulate plans for use in event of **atomic or other armed attack** were named last month by Governor Earl Warren.

Appointed to a **radiological safety advisory committee** were Dr. Stafford Warren, dean of the University of California at Los Angeles School of Medicine, Dr. B. M. Brundage, atomic energy project associate at the same institution, and Dr. Andrew H. Dowdy, professor of radiology at U.C.L.A., Dr. Robert S. Stone, professor of radiology at the University of California School of Medicine, Dr. Harold Hill, a San Francisco radiologist, Dr. Justin Stein, a Los

POSTGRADUATE EDUCATION NOTICES

For more complete information as to fees and time of sessions address the institutions as listed.

SEPTEMBER 1950

University of Southern California, School of Medicine

Clinical Review of Internal Medicine—12 weeks full-time from September 11 to December 1, 1950.

Cardiology and Vascular Disease—12 months, full-time from September 11, 1950 to September, 1951.

Hematology—12 weekly, 2-hour evening lectures. Clinical application of newer diagnostic methods in cardiology. Given at Los Angeles County Hospital.

Recent Advances in Surgery, Obstetrics and Gynecology—Given in San Diego.

Electrocardiography—Given at Centinela Hospital, Inglewood.

University of California, San Francisco

Ophthalmology—September 11 through 15, 1950. Toland Hall, University of California Hospital. Address: Stacey R. Mettier, M.D., Head of Postgraduate Instruction Medical Extension, University of California Medical Center, San Francisco 22.

University of California at Los Angeles

Symposia on Therapy in Metabolic, Endocrine and Gastrointestinal Diseases—September 20 to December 13, 1950. Wednesday evenings, 8 to 10 p.m.

Surgical Anatomy—September to December, 1950.

Stanford University, School of Medicine

September 11 to 15.

Morning Courses: Monday, Tuesday, Wednesday, Thursday and Friday, 8:30 a.m. to 12 noon.

Course 1—General Surgery
Course 2—Acute Surgical Emergencies
Course 3—Surgical Anatomy
Course 4—Internal Medicine
Course 5—Electrocardiography
Course 6—Diseases of the Chest
Course 7—Pediatrics

Afternoon Courses: 1:30 to 5 p.m.

Course 8—Surgical Anatomy
Course 9—Proctology
Course 10—Fundamentals of Roentgen Diagnosis
Course 11—Fractures
Course 12—Internal Medicine
Course 13—Obstetrics and Gynecology

Address: Stanford School of Medicine, 2398 Sacramento Street, San Francisco 15, California.

OCTOBER 1950

University of California at Los Angeles

Recent Advances in Obstetrics and Gynecology—One week.

NOVEMBER - DECEMBER 1950

University of California at Los Angeles

Ophthalmology.

DECEMBER 1950

University of California at Los Angeles

Internal Medicine—9 months full-time, December 4, 1950 to September 1951.

JANUARY 1951

University of California at Los Angeles

Advanced Hematology—Eight lectures.

* * *

TWO-DAY MEDICAL INSTITUTES, sponsored by the COMMITTEE ON POSTGRADUATE ACTIVITIES and by the local county society in each locality (exact dates to be announced later).

Santa Barbara in October 1950.

Fresno in November 1950.

Riverside in January 1951.

Santa Rosa in February 1951.

Sacramento in March 1951.

Angeles radiologist, Dr. John H. Lawrence, University of California associate professor of medicine and medical physics, and Dr. Phillip Condit of the State Health Department.

Physicians named to a **medical advisory committee** were Dr. Edward S. Rogers of Berkeley; Drs. Walter E. Macpherson, Harold Pearson, Justin J. Stein, George M. Uhl, and Richard M. Brundage, all of Los Angeles; Drs. Alonzo F. Brand, Earl R. Miller, and Rodney Beard, Adm. J. P. Owen, M.C., U.S.N. (Ret.), and Col. Kermit H. Gates, M.C., U.S.A., all of San Francisco; and Col. Paul C. Gilliland, M.C., 4th A.F., Hamilton Field.

* * *

A 16 mm. motion picture in color on **arthritis and rheumatism** is being made by the Arthritis and Rheumatism Foundation for showing at meetings of county medical societies and other medical groups. Produced under the supervision of the foundation's Medical and Scientific Committee, the film is scheduled for completion about September 1, 1950, and prints then will be available for loan to interested groups. There will be no charge save to cover shipping costs. In some areas, arrangements can be made through the foundation for medical speakers to address audiences at a showing of the film.

The film will review the incidence of the diseases, the economic and social significance of them, the lack of facilities for care of patients, and the small sums available for medical research, according to the foundation's announcement. Case histories in which cortisone and ACTH are used in treatment "will stress the fundamental importance of hormone therapy as a guide to fuller understanding of the disease processes in rheumatoid arthritis and gout."

Arrangements for borrowing the new film may be made through the secretary of the foundation, Dr. Charles Ragan, Presbyterian Hospital, New York 32, N. Y.

INFORMATION

Medical Technicians: The Present Need and Training in California

JAMES HOPPER, JR., M.D., and RAMONA GREEFKENS, *San Francisco*

THOSE individuals concerned with enlisting the services of medical technicians may have experienced considerable difficulty from time to time. This problem was present at the University of California Hospital throughout the war years and the situation has not been eased since. Adequately trained medical technicians continue to be scarce.

Conscious of the role that the state university should play in supporting and aiding the training of technicians, the faculty has reorganized and enlarged the medical technicians' curriculum (see Appendix I). However, it has been found that students eligible for our course are few in number. This has prompted investigation of the causes for the apparent shortages. With the aid of the Division of Laboratories of the State Department of Public Health, a survey was made to give an index of the need throughout the state for licensed medical technicians. Although made only by the simple expedient of a card questionnaire, the survey revealed facts which should be of interest to physicians, medical technicians, and others concerned.

On April 14, 1948, questionnaires were sent to 600 directors of laboratories in the state of California. Of the 340 answers received, 141 were from hospital laboratories and 199 from non-hospital clinical laboratories. The following is a summary of the questions and answers:

1. Q: How many positions in your laboratory require licensed technicians?
   A. 1,056 technicians were needed in the 340 laboratories.
2. Q: How many current vacancies have you?
   A: 153 vacancies in the 340 laboratories. (A shortage of 14.5 per cent.)
3. Q: What is your average yearly turnover of technicians?
   A: Approximately one-third of the total number of technicians employed.
4. Q: Are licensed technicians easily obtained?

A: *No*	*Yes*	*No Answer*
269 (79%)	49 (14%)	22 (7%)

5. Q: What is the quality of the technicians available?

A: *No. of Laboratories*	*Answer*
15	Excellent
75	Good
113	Fair
47	Poor
16	No technicians available
74	No answer

6. Q: Do you think that the state licensing requirements are excessive?

A: *No*	*Yes*	*Inadequate*	*No Answer*
263 (77%)	59 (17%)	3 (1%)	15 (5%)

This survey confirms the impression that there are not enough technicians available to fulfill the present needs in California. In the 340 laboratories there is a 14.5 per cent deficit of technicians. Secondly, the general quality of technicians appears to be only fair. Accordingly, most laboratory directors (77 per cent) do not think that the state license requirements are excessive; a small minority think they are inadequate. The rate of turnover in employment is extremely high. This may depend upon the fact that most medical technicians are marriageable women who are likely to give up their professional careers for marriage.

The following are some of the reasons which appear to be potent deterrents to the choice of medical technology as a career:

The appendix reveals that in order to take the California State Clinical Laboratory Technicians' Examination for licensure, it is necessary to have a college degree, or at least to have spent five years as a technician or apprentice in a laboratory approved by the state. Few laboratories are willing to give a five-year apprenticeship since the cost to themselves is likely to be excessive; they prefer to start with a college-trained novice. Such preparation should entitle the candidate to a good income. Yet, when one compares the economic status of medical technicians with that of other groups, it is immediately apparent that they are relatively low in the economic scale. Recent surveys* showed that a janitor gets from $36.40 to $57.67 for a 40-hour week, while a medical technician gets from $55.81 to $67.44 for a 40-hour week.† Whereas this salary may suffice for a single woman, it does not appeal to the average man who desires to raise a family. It is apparent that although educational requirements of technicians have steadily risen, their relative economic status has remained the same. Available records show that in 1936 medical technicians began at $85.00 a month, and that technicians who had seven years' experience were getting a salary of $105.00

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Administrator of Medical Technicians' Curriculum (Hopper); Supervisor of Medical Technicians' Curriculum (Greefkens).

*State of California, Department of Industrial Relations, Division of Labor Statistics.

†A weekly salary of $55.81 is paid to one who has had four years of college and one year of hospital apprenticeship, plus two years of practical experience. The top salary implies four to six years' additional practical experience.

a month, salary ranges which then, as now, compare to compensation for janitorial work.

It would seem that it is not alone insufficient remuneration which has led to the present dearth of technicians. Among other causes may be listed:

1. The lack of organized training programs or schools for the training of technicians. At present the Council on Medical Education and Hospitals of the American Medical Association lists only eight approved schools for apprenticeship training in California. These eight schools can accommodate only 64 students a year.

2. The failure on the part of organized groups (such as physicians and technicians through their societies, etc.) to create interest in the field, and to attract students. The field of medical technology is to be contrasted with that of nursing, in which (a) the Nurses Association sponsors a program creating interest in this field; (b) student nurses are subsidized during their training period in an amount sufficient for about three-fourths of their entire living expenses.

3. The fact that scientific development has created a need far outstripping the supply, a need which promises to grow as we advance into the age of increasing applied sciences.

4. The number of physicians in this state has approximately doubled in the past eight years, and the patient population has greatly increased.

It is hoped that the foregoing survey and comments, although incomplete, will serve to stimulate action by county medical societies and technician societies, favoring the lot of the student medical technician group. Physicians specializing in pathology particularly appear remiss in affording apprenticeship training to students qualified by appropriate university training to become technicians. Further, it is fair to point out that hospital administrators can expect a continued shortage of properly qualified technicians in the laboratories under their supervision, unless they fulfill their obligation by offering apprenticeships for student technicians. Since physicians are so dependent on technicians, the facts here disclosed should be a challenge to them to support any program which will increase the availability of competent technicians.

APPENDIX

I. *Requirements for Admission to the Medical Technicians' Curriculum, University of California Medical School:*

At least three years of college work, including Biochemistry 101 and Bacteriology 101, or the equivalent of these courses.* Preference is given to applicants who hold a degree of A.B. or B.S. with a major in one of the biological sciences, and who have completed the prescribed courses stated above.

II. *Requirements for Entrance into the Examination for California State Licensure:*

(a) Completion of a regulation four-year college curriculum in medical or clinical laboratory technique with a degree of A.B. or B.S. in a college or university approved by the department (State Department of Public Health), the last year of which course shall have been primarily clinical laboratory procedure; provided, however, that if the curriculum did not include practical clinical laboratory work, six months of apprenticeship in a clinical laboratory approved by the department shall be required; or

(b) Graduation from college with a degree of A.B. or B.S. and a major in bacteriology, biochemistry, or essentially equivalent subject or subjects as may be determined by the department, plus one year of apprenticeship training in a clinical laboratory approved by the department. A year of apprenticeship training in a public health laboratory may be accepted if the apprenticeship or university course included practical work in clinical biochemistry and hematology; or

(c) A minimum of five years' experience as a technician or apprentice doing clinical laboratory work embracing the various fields of clinical laboratory activity in a clinical laboratory approved by the department, except that university work which includes courses in the fundamental sciences may be substituted to a maximum of four years for such experience in the ratio of 30 semester hours for each year of experience.

III. *Requirements for Admittance to the Examination of the Registry of the American Society of Clinical Pathologists:*†

At least two years of college work, including the following curriculum:

Biology: 12 semester hours, of which 4 semester hours must be zoology.

Chemistry: General inorganic: 8 semester hours, including 4 semester hours of laboratory. Quantitative analysis: 4 semester hours, with not less than 1 semester hour of laboratory.

Electives: Sufficient to give a total of 60 semester hours of college credit, *plus* at least 12 consecutive months in a school of medical technology approved by the Council on Medical Education and Hospitals of the American Medical Association.

IV. *Medical Technicians' Curriculum — University of California Medical School:*

The University of California Medical School offers a training program to students preparing to be

*Note, however, that the State of California requires either an A.B. or B.S. degree in order for the applicant to be eligible to take the state examination, thereby making it possible to gain a license to practice medical technology. Accordingly, unless the college attended by the student is willing to allow credit toward the A.B. or B.S. degree for the practical year spent in the University of California Medical School course, it is necessary to obtain a degree prior to taking the course.

†It will be noted that the California State requirements and those of the University of California Medical School are distinctly higher than those of the Registry of Medical Technologists; consequently, if one is prepared to take the State examination, he is also eligible for the Registry examination.

medical technicians. The curriculum is given in the form of a practical rotating apprenticeship, which is one year in length, and covers training in medical bacteriology, biochemistry, clinical pathology, serology, blood bank procedures, parasitology, mycology, histological technique, basal metabolism and electrocardiography. This course is offered under the supervision of the administrator of the medical technicians' curriculum of the School of Medicine; the laboratory work performed by the students is under the guidance of the graduate technicians and certain faculty members of the Medical School. The students are assigned for allotted periods to the various clinical and teaching laboratories of the Medical School and associated institutions.

Upon satisfactory completion of the course, the student receives a certificate in laboratory technique, and is eligible for the National Registry Examination. If the student holds a degree of A.B. or B.S., he is eligible for the California State Examination.

Practices of Life Insurance Companies in Payment of Medical Fees for Examinations*

In November of 1949 a letter was addressed to all insurance companies licensed to write life insurance in the state of Wisconsin, directing their attention to the desirability of examining their fee schedules for the payment of medical services rendered in the examination of persons applying for life insurance. This communication was directed to insurance companies at the suggestion of the Bureau of Economic Research of the American Medical Association, which organization had been urging insurance companies to revise their fee schedules in line with increased living and business costs of physicians rendering this service to insurance companies.

On the basis of the many replies received to the initial communication it was apparent that many companies had revised their fee schedules within recent years, or were considering such revisions in line with the suggestion made by the American Medical Association and the State Medical Society of Wisconsin. To what extent such revisions had been made, and a comparative picture of prevailing practices among the leading insurance companies doing business in Wisconsin, was not apparent from the replies received, and it was suggested that a more detailed study be made, so as to provide a better understanding of prevailing practices, and to determine to what extent basic changes had been made in fee schedules during the past 20 years.

As a result of this request a second communication was sent to all 52 insurance companies licensed to write life insurance in Wisconsin, with a brief questionnaire attached. The content of this questionnaire was suggested by Dr. Nels Hill, Madison, who has had wide experience with the content of insurance examinations.

On the following pages are given some summary statistics which will serve to provide a better understanding of prevailing fees charged for the more basic medical services rendered life insurance companies.

In reviewing this material it must be recognized that the statistics are not as complete as would be the case in a longer and more detailed study. In many instances the company reporting indicated that fees varied within stated or unstated ranges, depending upon the amount of information required of the company, or the various types of forms used. Thus, there is a variation of practices which could not be completely reflected in the brief summary prepared. However, some general basic principles can be attained from even so elementary a study as was carried on.

1. *There have been many increases in fees.* In many cases these increases have been rather small, but it is obvious that many of the insurance companies have recognized the justice of paying more for the services rendered in 1950 than the rendition of the same services in 1940 and 1930.

2. *Varying risks, varying fees:* While most companies report a basic fee for an average examination the larger risks necessitate special examinations which are reflected in more complicated and complete medical services, which in turn are reflected in higher fees.

3. *Trend towards "fees as billed":* While the simple procedures have rather set fees, the special services are increasingly billed on the basis of service rendered, and are not restricted at a set fee. There is often range, but more frequently the determination of the fee charged is left up to the physician rendering the service. This is particularly true in services involving chest x-rays, electrocardiograms and fluoroscopic examinations.

4. *Lower fees for Wisconsin companies:* Generally speaking, the Wisconsin companies do not pay as high fees as do the companies with offices outside of the state. Several of the Wisconsin companies have indicated that they were considering a marked revision of their present fee schedules, which might bring them in line with the companies with home offices outside of the state.

The summary given below covers the reports of 39 out of 52 insurance companies. With few excep-

*A study made for the Interim Committee of the Council of the State Medical Society of Wisconsin during January and February 1950.

tions the companies not reporting are small in their operation of life insurance departments, so the reports of the 39 companies responding to the request for information present a very satisfactory basis for comparison.

1. *Regular Medical Examination*

39 companies reporting

Present Fees:

Range $3 to $7.50

1—$3 (Wisconsin State Life Fund. Rate set by law.)
24—$5
14—$7.50

Eight companies report varying fee according to extent of risk. Most of those reporting varying fees give up to $10 on special risks. Fourteen companies report increase from $5 to $7.50 since 1930 or 1940.

* * *

2. *Medical Examinations Plus Heart Report*

35 companies reporting

Present Fees:

Range from $5 to $13

1—$5
1—$6
10—$7
4—$7.50
9—$8
4—$9
4—$10.50
1—$11.50
1—$13

In most instances $2 to $3 is added to the fee for a regular examination if special heart form required. Several companies report varying fee for special policies over $25,000. Twenty-one companies report some increase in fees for heart reports since 1930 and 1940. In prior periods, in many instances this service was considered as part of the regular examination, without additional remuneration.

* * *

3. *Additional Fee for Urinalysis*

36 companies reporting

Present Fees:

Range from $1 to $3

13—$1
20—$2
3—$3

} In all instances, only securing of specimen. Analysis made at home office.

Eight companies report increase since 1930-40. Increase in all instances an additional dollar.

* * *

4. *Postage for Mailing of Specimens*

36 companies reporting

Present Fees:

29—Postage paid by company or refunded to physician.
7—No postage paid.

Of the companies paying postage, five report that in 1930 or 1940 such expense was borne by the physician.

* * *

5. *Juvenile Examinations*

32 companies reporting

Present Fees:

Range from $2 to $10

2—$2
3—$2.50
15—$3
1—$4
9—$5*
1—$7.50*
1—$10*

Ten companies report an increase in fees from 1930 and 1940.

*Several report higher fee for combination of juvenile and payor examinations. While not indicated on the reports, the fees in excess of $4 are probably a combination of juvenile and payor examinations.

6. *Payor Examinations*

29 companies reporting

Present Fees:

Range from $2 to $7.50

1—$2
1—$2.50
7—$3
1—$3.50
3—$4
12—$5
4—$7.50

As in juvenile examinations, many quoted fees above $3 are for combinations of juvenile and payor examinations. Seven companies now having an established fee for payor examinations did not have in 1930 and 1940. Nine companies that did have established fees for payor examinations in 1940 have since that time increased their fees.

* * *

7. *Family Physician Blanks*

34 companies reporting

Present Fees:

Range from $1 to "fee as requested"

1—$1
18—$2 (or from $2 to $3)
11—$3 (or from $3 to $5)
4—"as billed"

Several companies report varying fees, either based on (1) length of report required, (2) larger fee for large clinics such as Mayo's. Seventeen companies report increase over fees paid in 1930 and 1940 (increases usually $1).

* * *

8. *Glucose Tolerance Tests (Urine Only)*

13 companies reporting fees by specific amounts
5 companies reporting fees "as billed"
16 companies reporting "not used"

Present Fees:

Range from $2 to "as billed by laboratory"

4—$2
1—$2.50
5—$3
1—$5
1—$7.50
1—$10 (if lab. work done by M.D.)
5—"as billed"

Two companies report increase ($1) in fee over fee paid in 1940. There is a tendency to drop this from fee schedules by several of the companies reporting.

* * *

9. *Glucose Tolerance Tests (With blood sugar determination)*

26 companies reporting specific fees
9 companies reporting fees "as billed by laboratory"

Present Fees:

Range from $5 to $15

The fees above $7.50 are generally determined on the number of leads requested and furnished. The lower fees are generally for collecting sample only (laboratory work done in the home office).

9—$5 (for collecting)
2—$7 (for collecting)
1—$7.50 (for collecting)
1—$8
11—$10
1—$12
1—$15
9—fees "as billed by laboratory"

Six companies report an increase in fees since 1930 and 1940. Trend seems to be away from fee for laboratory analysis and payment of $5 to $7.50 for collection of sample, which is then analyzed in home office laboratory or in a laboratory designated by the company.

10. *Electrocardiogram*

35 companies reporting
24 companies reporting specific fees
11 companies reporting "fee as billed"

Present Fees:

Range from $5 to $15

Many reports have ranges, with fees determined on whether direct or chest, or a combination. Higher fees also involve interpretation. (One company reports, "We pay up to $30 for specialized examinations on large risks, including chest x-ray."

3—$5 "and up"
10—$7.50 "and up" (generally up to $10)
11—$10 "and up" (generally up to $15)
11—"fee as billed"

Fourteen companies report an increase in fees over 1930 and 1940. In most instances the increase has been in a recognition of varying fees for varying services. Generally the increase has been between $3 and $7.50 over fees paid in 1940.

* * *

11. *Chest X-rays*

35 companies reporting
23 companies reporting specific fees
12 companies reporting "fee as requested"

Present Fees:

Range from $5 to $15

3—$5 "and up"—range up to $15
18—$10
2—$10 to $15
12—"fee as requested"

Four companies report an increase in fees over 1930 and 1940. In most instances the increase has been in recognition of varying fees for varying service. The most common fee in 1940 as in 1950 was $10.

* * *

12.* *Fluoroscopic Examinations and Orthodiagram*

33 companies reporting
11 companies reporting specific fee
11 companies reporting "fee as requested"
1 company reporting "fee varies"
10 companies reporting "never requested"

Present Fees:

Range from $5 to $15

3—$5
1—$5 to $10
5—$10
1—$10 and up
1—$15

For this service there have been two companies reporting specific fees which indicate an increase in rates over fees paid in 1940. Trend seems to be to have fee set by physician or laboratory rendering the service. There were more companies reporting non-use of this service than any other procedure listed.

BOOK REVIEWS

TEXTBOOK OF PEDIATRICS. Edited by Waldo E. Nelson, M.D., Professor of Pediatrics, Temple University School of Medicine, with the collaboration of 63 contributors. Fifth edition with 426 illustrations, 19 in color. W. B. Saunders Company, Philadelphia, 1950. $12.50.

The fifth edition of Mitchell and Nelson's "Textbook of Pediatrics" represents a thorough going-over and perfecting of the widely accepted fourth edition. Each chapter has been thoroughly revised and rewritten and many new chapters have been added. Improvements worthy of mention which are in keeping with the need for background knowledge in the care of children are the chapters on "Growth and Development" and "Mental and Emotional Development." These chapters have been thoroughly rewritten and enlarged upon, providing a most excellent orientation to the "pediatric way of thinking" in the application of medical knowledge to infants and children.

Of particular interest is the handling of the chapters "Disturbances of Fluid and Electrolyte Equilibrium" and "Parenteral Fluid Therapy." These subjects, always difficult to present clearly, have been presented in a brief, concise, and practical manner. The student as well as the practitioner can find a quick qualitative and quantitative answer to diagnostic and therapeutic problems in acid-base and dehydration disorders.

In an effort to make the textbook eminently practical, each author, in addition to the didactic dissertation of the specific disease, has presented clear-cut therapeutic programs for the handling of the specific disease. The quality of the text was present in the first three editions under the editorship of Griffith and Mitchell and has been successfully maintained and improved upon by Nelson. Finally, of great value is the presence of an appendix which provides ready reference to normal blood and urine values in infants and children of various ages. Included are normal cerebrospinal fluid values; water, salt, and nutritional requirements for infants and children; food value tables; methods of diet calculation, nomograms for surface area, height and weight; and a variety of conversion tables always necessary to the busy student and practitioner with a limited library at hand.

In the fifth edition of the Mitchell and Nelson "Textbook of Pediatrics" it is apparent that every effort has been made to provide a most up-to-date, complete, and practical textbook of medicine as it relates to infants and children. It should have no difficulty in maintaining its position as an outstanding textbook of medicine, and will be of value not only to the student and pediatrician but to others in all fields of medicine.

* * *

THE ARTHROPATHIES—A Handbook of Roentgen Diagnosis. By Alfred A. DeLorimer, M.D., Radiologist, St. Francis Hospital, San Francisco, formerly Commandant, the Army School of Roentgenology. Second edition. The Year Book Publishers, Inc., 200 East Orange Street, Chicago. 1949. $7.00.

This second edition of this book, one of a series of monographs on roentgenological topics, has been augmented with more written material. Several new illustrations are used, and the system of marking indicators has been clarified. The book is in three major parts: The peripheral joints, the spine, and temporomandibular joints. Emphasis is placed on the appearance of the soft tissues as well as the bones, for soft tissues often show earlier manifestations of the disease. Common technical errors are discussed, and the value of high KV technique is argued. Considerable material which is primarily bone disease is discussed because of associated joint involvement. The book is organized to make ready reference easy. Despite the small size of the book, its cuts are satisfactory, and this volume is one which should prove of interest and value to all radiologists and others interested in joint disease. Dr. DeLorimer has threaded his way through the maze of different joint diseases in a clear and succinct manner.

* * *

MEDICAL DISEASES OF THE KIDNEY (An Atlas and Introduction). By J. F. A. McManus, M.D., Associate Professor of Pathology, the Medical College of Alabama, Birmingham. Lea & Febiger, Philadelphia, 1950. $6.00.

The backbone of this small book consists of one hundred large illustrations of renal lesions, virtually all of them photomicrographs and most of them showing details of kidney tissue as stained by the periodic acid—Schiff's reagent technique. The illustrations are beautiful, revealing structure never before seen by at least one reader. It is perhaps not the fault of the stimulating text that its quality is not quite up to that of the illustrative material. One hopes the typographical errors will be corrected in later editions. The work is highly recommended specifically to all who are interested in renal lesions and to all thoughtful physicians.

* * *

CLINICAL NEUROLOGY. By Bernard J. Alpers, M.D., Sc.D. (Med.), Professor of Neurology, Jefferson Medical College, Philadelphia. 240 Illustrations. Second Edition. F. A. Davis Company, Philadelphia, 1949. $9.50.

The second edition of this textbook of neurology presents few departures from the original, but in general has been adequately brought up to date in a field that is evolving a more dynamic concept in recent years.

The book is rather more complete than the usual text, and may be considered rather voluminous for the medical student not contemplating specialization in neurology. However, the section devoted to examination of the nervous system is very good, and for this reason the book is especially valuable to the student. Equally, it is sufficiently complete to serve as a reference work adequate to the practititioner who, although not a specialist, needs to treat patients with neurological disease.

The form of presentation used is simple and direct. There is perhaps a tendency for dogmatic statements in fields in which some controversy remains, but this is not a serious disadvantage to the student, and allowances may be made for it by the neurologist. The work is probably as good a single volume text on neurology as is at present available.

* * *

METHODS IN MEDICAL RESEARCH—Volume 2. By J. H. Comroe, Jr., M.D., Editor-in-Chief. The Year Book Publishers, Inc., 200 East Illinois Street, Chicago, Illinois. 1950. $6.50.

The first volume in this series was reviewed favorably, even enthusiastically, in CALIFORNIA MEDICINE. The present volume is up to the high standard set by the earlier one.

The first of the three sections in this book deals with methods of study of the bacterial viruses (the bacteriophages) for 73 pages. The next section devotes 170 pages to pulmonary function tests (the topics include measurements upon respired gases, measurements on arterial blood, and specific tests of pulmonary function). The third section (97 pages) deals with the assay of certain hormone secretions, with particular reference to anterior pituitary hor-

mones, ovarian hormones, and testicular and adrenal hormones.

As in the first volume, each subdivision is written by an authority and is reviewed and commented upon by others. Methods are presented in great detail, and there are adequate bibliographies, author index and subject index.

The book is recommended to all medical libraries and to those interested in the study of disease, particularly to microbiologists, gynecologists and other endocrinologists, and to those concerned with pulmonary function.

* * *

AETIOS OF AMIDA—The Gynaecology and Obstetrics of the VIth Century A.D. Translated by James V. Ricci, A.B., M.D. The Blakiston Company, Philadelphia, 1950.

Aetios of Amida was a wise man, for he collected all that was known of the medical treatments of his time. He knew of strange remedies and powerful magic. He must have practiced the art of healing with skill and success, for he rose to the position of court physician to the first Justinian, the greatest of the emperors of Byzantium. Aetios was more than a mere healer, he also was a great and astute recorder of the accumulated knowledge of his period. This he set down in the 16 volumes of the Tetrabiblon, which from 600 to 1600 A.D. remained one of the few great medical encyclopedias of the old world. The last volume was devoted exclusively to the treatment of women. The indefatigable Dr. Ricci considered it important enough for posterity to rescue old Aetios' recommendations for the entertainment of his colleagues, perhaps with tongue in cheek, because now as then fact and fancy so often become entangled in the practice of gynecology and obstetrics. If you do not believe it, just have a look at what old Aetios had to say about the treatment of sterility.

Book reviews come at a dime a dozen and most of them are never read by the busy doctor. But if you are one of those who prove the exception to the rule, take my word for what I have to say about Ricci's sincere effort to open the past to you, even if for no other reason than to stimulate your imagination. As far as the humble opinion of your reviewer is concerned, Ricci has succeeded admirably in doing just that with his translation of Aetios' admonitions. Like some of the other historical contributions from the pen of James V. Ricci, this book is dressed in meticulous English and embellished with a multitude of annotations and comments. The author has been fair with the original text and whenever there was more than one meaning to a statement he kept the translation as literal as possible after consulting other experts of the lingua Latina. There is nothing in this book that is of practical value to the physician of today, but the philosophical implications and deductions incidental to medical recommendations are priceless gems of pristine thinking.

Students of history, teachers and thinkers will enjoy this book. It is a storehouse of ancient thought and of some profound wisdom, but it also is an important historical document of the evolution of medical practice. There are 123 chapters in the 16th volume of the Tetrabiblon, but the translator has managed to set them down in readable English in only 120 pages. For those who like to browse through source references and extracts from the original text, Ricci supplies 100 pages of interesting annotations. Arturo Castiglione, professor of gynecology at the University of Milan, Italy, has written a fitting introduction. The Blakiston Company of Philadelphia presents the little tome to the profession in an attractive binding. The translator has used the Latin edition of Coronarius published in Basle, Switzerland, in 1542 by Froben as the original source for his latest contribution to the history of gynecology and obstetrics. Your reviewer considers "Aetios of Amida" a worthy addition to your shelf of books to be read during leisure hours.

SPEECH THERAPY FOR THE PHYSICALLY HANDICAPPED. By Sara Stinchfield Hawk. Stanford University Press, Stanford, California. 1950. $4.00.

This book is of special value for speech therapists and fills a gap for every physician who treats spastic children. Speech therapy has been part of the treatment given to handicapped children at the Orthopaedic Hospital in Los Angeles for several decades. The author describes procedures and results in 53 cases during an eight-year period. From the clinic of the hospital, 9 per cent of the patients had speech defects (against 2 per cent of normal school children). The other therapeutic procedures, including braces and physiotherapy, were used in coordination with speech treatment.

The book contains a wealth of exercises for relaxation, practice words and sentences, articulatory exercises and verses for speech training of spastics. The occurrence of stuttering is high among handicapped children as result of poor adjustment. Therapeutic procedures and rules of mental hygiene are well outlined.

In 49 per cent the author found pure left-handedness or mixed left and right-handedness which in her opinion accounts for inabilities in speaking, reading, spelling and writing as well as for clumsiness. The I.Q. improves, often fast, under speech training. Dental factors in spastics due to malocclusion or "side-bite" from stronger pull exerted by the facial and neck muscles on the uninjured side cause need for corrective dentistry and speech training.

An interesting chapter is added on personality measurements and vocational guidance for handicapped children. I. Q. tests are difficult to apply; verbal expression is handicapped by speech difficulties, performance tests by manual incoordination. The description of combined methods will be of great practical help.

* * *

HANDBOOK OF OBSTETRICS AND DIAGNOSTIC GYNECOLOGY. By Leo Doyle, M.S., M.D. Illustrations by Ralph Sweet. First Edition. University Medical Publishers. P.O. 761, Palo Alto. 1950. $2.00.

Dr. Leo Doyle's "Handbook of Obstetrics and Diagnostic Gynecology" is a concise outline of these fields of medicine. The author states that his book is neither a textbook nor a reference book; rather, the information is outlined so that it is easily and quickly available to the busy practitioner. It is planned that the handbook will undergo frequent revisions to keep pace with the inevitable changes of therapeutics. Descriptions of surgical techniques have been omitted.

The book is divided into two sections. The first section on obstetrics includes the essentials of diagnosis and treatment of normal and abnormal pregnancy. The Rh factor is presented in a manner by which the physician can readily grasp the intricacies of this puzzling problem. There is an excellent discussion of the emotional aspects of pregnancy—a facet of patient care which has had increasing emphasis in the literature in recent months. A chapter is included on minor problems of pregngancy; the vexing nausea and vomiting, hemorrhoids, constipation and others with to-the-point methods of treatment which will be welcomed by obstetricians.

The section of diagnostic gynecology is rather short and does not cover the material as thoroughly as the obstetrical section. The diagnosis of pelvic masses and infertility management are well presented.

The diagrams and illustrations throughout the book are adequate to augment the accompanying text.

There is an excellent table of normal blood chemistry and urine values and the variations occurring in pregnancy on the cover pages, which is an added bonus of this very worthwhile book. Dr. Doyle's handbook will be a welcome addition to the libraries of general practitioners who have particular interest in obstetrics and gynecology.

BEDSIDE DIAGNOSIS. By Charles Mackay Seward, M.D., F.R.C.P. (Edin.). The William and Wilkins Company, Baltimore, 1949. $3.50.

This little book has been written to provide an analytical and systematic aid in the process of differential diagnosis. The author bases his text on the concept of disease as a disturbance of function, which may or may not be accompanied by structural change. He emphasizes that the causes of diseases are often indicated by the grouping and the method of development of symptoms and signs. His approach and discussions are very rational, viewing the patient as a whole and not as a number of separate compartments.

There are 22 chapters, each taking one of the common dominant symptoms of disease as a nucleus for discussion.

The reviewer finds fault with certain omissions and statistics. The common and important symptom of coma deserves consideration as a chapter heading. And, although the author usually accents the role of functional disorders, he quotes such conditions as being responsible for only 28 per cent of pain in the epigastrium (p. 61), whereas peptic ulcer is responsible for 59 per cent of gastric symptoms in hospital patients (p. 71). These percentages certainly seem weighted.

In general, however, this is an excellent book. It is recommended primarily as a teaching guide but can be of considerable service as a quick reference for the practitioner's diagnostic problem.

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EXHIBITIONISM. By N. K. Rickles, B.S., M.D., Fellow of the American Psychiatric Association, Diplomate of the American Board of Psychiatry and Neurology, Senior Consultant at the Veterans Administration Center, Los Angeles, Consultant in Psychiatry to the Office of the Surgeon General, Medical Department, United States Army, and Director of the Psychiatric Center of Seattle. J. B. Lippincott Company, Philadelphia, 1950. $5.00.

In the introduction, the author states, "This is not intended to be, in any sense, the final or definitive treatment of the subject." With this the reviewer can agree, since reading the book leaves one with no very clear idea of the genesis of exhibitionism or its treatment.

The author's thesis is that exhibitionism in the male is a normal primitive phenomenon which has been banned by the process of civilization. The repression of this urge, which is accomplished by most individuals before adulthood is reached, fails in the exhibitionist, and the reason for this failure is traced to revolt against a dominating mother.

The whole approach to the problem is from the psychoanalytical viewpoint and would not be acceptable to all psychiatrists not so trained. The idea that exhibitionists are suffering from mental illness and should receive psychiatric treatment we can certainly not quarrel with, although the low yield of therapeutic results can be seen from the account of some of the author's cases contained in the appendix.

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MEDICAL GYNECOLOGY. By James C. Janney, M.D., Associate Professor of Gynecology, Boston University School of Medicine, Associate Visiting Gynecologist, Massachusetts Memorial Hospitals — Second Edition — Illustrated. W. B. Saunders Company, Philadelphia, 1950. $6.50.

Your reviewer has often wondered why there should be a division between medical and surgical gynecology since the two are inseparable and must be taught as a unit of general medicine. Most of the books labelled "Medical Gynecology" do not stick to their purpose but devote considerable space to surgical procedures without presenting adequate details. Janney's "Medical Gynecology" is no exception. As the author says himself, the book is the result of a series of lectures for medical students and your reviewer comes away with the feeling that no other merit is attached to this book, although it is meant "to be a refresher for the general practitioner to bring him up to date on the newer developments in the field." Your reviewer has looked diligently through the subject matter and admits reluctantly that he found little that could not be read more profitably in any standard textbook or even in the much maligned but very handy little compends called "Office Gynecology." What a pity that the author did not purge his brain-child of many archaic notions before presenting it again to the medical public in a made-over dress. For example, who ever would agree with the statement that cervicitis is a common source of bleeding and that astringent tampons are beneficial in treating the relaxed outlet? Your reviewer's strictly personal reaction to Janney's "Medical Gynecology" is that it has little to offer that is not treated more adequately and authoritatively in any of the well known gynecologic texts.

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RECENT ADVANCES IN CHEMOTHERAPY. By G. M. Findlay, C.B.E., Sc.D., M.D., F.R.C.P., Editor, Abstracts of World Medicine and Abstracts of World Surgery, Gynaecology and Obstetrics, British Medical Association. Third Edition. The Blakiston Company, Philadelphia, 1950. $7.50.

This volume is by far the best and most comprehensive review of chemotherapy of parasitic diseases that has appeared thus far. Unfortunately, the advances in chemotherapy have been so extensive that it is not possible to review them all in a single volume. Thus, the third edition of Findlay's "Recent Advances" is Volume I of a four-volume series. It contains the chemotherapy of scabies and of helminthic and protozoal diseases with the exception of malaria.

The author has covered the world literature in an amazingly precise fashion. Since the volume is well indexed and contains most of the pertinent references in the fields of chemotherapy covered, it is possible for the physician and student to consult original sources. Most important is the presentation of a more balanced view toward the role of chemotherapy and the exposition of the development of drug resistance by parasites which are pathogenic for man.

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THE PHYSIOLOGIC BASIS OF MEDICAL PRACTICE —A Text in Applied Physiology. By Charles Herbert Best, C.B.E., M.A., M.D., D.Sc.(Lond.), Professor and Head of Department of Physiology, University of Toronto; and Norman Burke Taylor, V.D., M.D., F.R.S.(Canada), F.R.C.S.(Edin.), M.R.C.S.(Eng.), L.R.C.P.(Lond.), Professor in the History of Medicine and Medical Literature, University of Western Ontario. Fifth Edition. The Williams and Wilkins Company, Baltimore, 1950. $11.00.

Since its first edition appeared in 1937, this book has been regarded much as a "medical bible," and it remains so today. In this, its fifth edition, it still gives more information about the physiological basis of medical practice than any other book—even though it appears less oracular in 1950 than it did in 1937.

This edition has had fairly extensive revision, done for the most part by Dr. Taylor, but a considerable part of the material of earlier editions has been retained. This gives rise to a certain amount of unevenness in the text. The ratio of misspelled words is fairly high (for example, on page 658 the word metabolism is misspelled in the heading for chapter 50).

It is still highly recommended to all students of medicine, including the practicing physician who wishes a clearer understanding of the basic facts involved in his practice.